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Identifying Menstrual Symptom Patterns in Young Women Using Factor and Cluster Analysis

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A Thesis Presented

by

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ABSTRACT

IDENTIFYING MENSTRUAL SYMPTOM PATTERNS IN YOUNG WOMEN USING FACTOR AND CLUSTER ANALYSIS

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Approximately 80% of reproductive age women experience physical or emotional symptoms prior to onset of menses. Of these women, approximately 20% experience symptoms severe enough to interfere with social functioning and life activities and meet criteria for premenstrual syndrome (PMS). More than 100 different symptoms are associated with PMS, the most common of which include breast tenderness, headache, anger, and depression. Symptom groupings tend to be stable within an individual but can vary distinctly between women. Potential differences in the etiology of symptoms suggest that PMS should not be considered a single condition in research or clinical studies, but rather may represent distinct entities that group by symptom patterns. The primary goal of this study was to identify symptom patterns using factor and cluster analysis. Analysis included: 1) a cohort of healthy women aged 18-30 (n =414); and 2) the subgroup of women meeting established criteria for PMS (n=80). All participants provided information on the occurrence and severity of 26 menstrual symptoms by validated questionnaire. Four distinct symptom patterns emerged: Emotional,

Psychological, Physical, and Consumption. Cronbach's alpha levels demonstrating reliability were high in both the total population (0.71 – 0.90) and in the PMS subset (0.69-0.80). Additionally, cluster analysis identified 4 clusters in both the total population and PMS subset. These symptom patterns were consistent with those identified in prior studies in diverse populations. These observations suggest that distinct subtypes of PMS may exist, and should be considered when recommending treatments and evaluating risk factors.

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CHAPTER I

INTRODUCTION

Introduction

There are over 150 different premenstrual symptoms that are associated with a woman's menses covering a wide range of cognitive, behavioral, physical, and emotional disturbances.[1-3] Common examples of these symptoms include, but are not limited to: confusion, mood swings, food cravings, breast tenderness, headache, abdominal cramping, anger and depression.[3-7] These symptoms are present in the luteal phase and absent during the follicular phase of the menstrual cycle and can be present at any time during the reproductive years of women. Symptoms usually last 3-5 days, but may persist up to 10-14 days per month.[1-2, 8-11]

It is estimated that approximately 80% of women of reproductive age experience physical or emotional premenstrual symptoms.[6, 8-9, 12-13] The prevalence of premenstrual symptoms tends to increase in the mid-20s to the mid-30s.[8] The symptoms and their severity can vary substantially between women and many evaluations suggest stability within a woman's menstrual cycle which is important for being able to identify patterns.[3-4, 10, 14-16] An estimated 50% of women who experience symptoms seek medical care and 45% have asked for help with symptoms.[8, 11-12, 17] It is estimated that the common treatments for premenstrual symptoms have less than 60% efficacy.[8, 17] The most common treatment options for women are selective serotonin reuptake inhibitors (SSRIs), oral contraceptives, alprazolam, dietary supplements, and psychological treatments.[8-31] It has been recommended by several studies that the identification of symptom clusters and

the identification of the underlying factors of these clusters will assist in clinical diagnosis and possible personalization of treatments.[7-9, 14]

Classification of PMS and Diagnostics

The prevalence of premenstrual symptoms in the general population is important to understand, as is the prevalence in the sub-population of women that experience more severe forms of disease, premenstrual syndrome (PMS) and premenstrual dysphoric disorder.

The prevalence of PMS has been reported by the American College of Obstetricians and Gynecologists (ACOG) to be between 15 to 20% of U.S. women of reproductive age but has been reported to be as low as 8.3% and as high as 31%.[5, 20-21] Variations in diagnostic criteria and measurement instruments leads to inconsistency in prevalence estimates. One example of the difficulty with diagnostics is that there are guidelines from the ACOG and World Health Organizations (WHO) which are not always consistent with each other. ACOG designated a set of diagnostic criteria for PMS in 2000. The diagnostic criteria include experiencing (1) at least one affective and one somatic symptom during the 5 days prior to menses during the 3 prior menstrual cycles, (2) symptoms end within 4 days of the onset of menses and do not return until at least the 12th day of the cycle, (3) interfere with social, school, and work activities, and (4) symptoms are present in the absence of pharmacological therapy, hormone ingestion, or drug/alcohol use.[42]

Pathophysiology of Symptoms

It is common for women to experience a cluster of symptoms for which one treatment may reduce the severity of some of the symptoms but not all of the symptoms. These symptom clusters can include a few symptoms to more than 10 distinct symptoms.[4, 7-9, 15-17] But many studies have found that even though the symptom numbers may vary between women that the symptoms, particularly those that are more severe, are persistent across cycles within women.[7-8, 19-20, 36] The pathophysiology of premenstrual symptoms and PMS are not well understood but they are thought to be due in part to cyclical changes in sex steroid hormones. For example, a spike in estrogen levels occur in the follicular phase and a spike in progesterone levels occur in the luteal phase prior to menstruation.[10, 37-38] Symptoms that are described with the large fluctuation in progesterone are generally mood disturbances. [37] But these changes most likely do not account for the wide array of symptoms that are seen between women and even in the same woman. [14,20,39]

Some of the physical symptoms associated with PMS likely involve dysfunction of the renin-angiotensin-aldosterone system (RAAS). This system is associated with fluid and salt retention because it causes the adrenal glands to secrete aldosterone and has been reported with symptoms like swelling of extremities and bloating of the abdomen.[18,21] While other menstrual symptoms like headache, muscle pain, and breast tenderness, are not well understood.

It is proposed that some symptoms are affected by hormonal shifts while others may be affected by changes in neurotransmitters.[3,5,10,21,37-38] The severe emotional,

cognitive, and behavioral premenstrual symptoms associated with PMS have been hypothesized to be affected by changes in neurotransmitters. The neurotransmitter serotonin has been examined in part because of pharmacological therapies, like selective serotonin reuptake inhibitors (SSRIs), which utilize it as an antidepressant and anxiety reducer. [10,14,20,28]

Treatment of Premenstrual Symptoms and PMS

Currently, the diagnostic criteria set forth by ACOG and WHO, identify PMS as a single disorder. This identification hinders effective treatments, treatment options for individuals, and studies of the etiologic factors. Treatment options currently involve diet change, behavioral modification, and pharmacological interventions.[9-10,18,21-24] The dietary interventions include diet and nutrition restrictions/supplementations and the behavioral interventions include psychological therapies.[9,18,21] The pharmacological interventions include the use of SSRIs[9-10], oral contraceptives[9-10], gonadotropin-releasing hormone agonists[10], alprazolam[9], and many others. [21] These treatment options are helpful for some symptoms. For example, dietary treatments that include calcium[22,25], B6[9,20,26], and magnesium supplementation[20,30] have shown to improve some symptoms. However, supplementation of evening primrose oil has been shown to be ineffective in treating symptoms.[18,27] Clinical trials show that oral contraceptives are effective for some of the somatic symptoms, such as breast pain and bloating, but these have also been shown to have deleterious effects on psychological symptoms in some studies. [30] Additionally, clinical trials that show SSRIs are effective for treating some of the emotional and somatic premenstrual symptoms but long term use of these medications can be financially costly and are known to have adverse effects.[9,18,28]

Economic Costs

With approximately 20% of U.S. women of reproductive age experiencing the detrimental effects of PMS, it is expected that there would be societal and individual economic costs in addition to the cognitive, behavioral, physical and emotional disturbances. [5, 20-21] In 2005, one study estimated the direct and indirect economic costs. The authors found that in addition to the direct medical costs of approximately $59 per woman per year of PMS, there is an added estimated $4,000 in indirect costs per woman per year.[43] The extra indirect costs are attributed to reduced work productivity and missed workdays. The low efficacy of treatments, severity of symptom complaints, and economic burden on individuals and society indicate a need to further research new methods of identification and diagnosis of premenstrual symptoms in both the general population and in the sub-population of women that experience PMS.[6,43-44]

Epidemiology

Eight epidemiological studies have investigated premenstrual symptom clusters in women. Three of these studies were cohorts [4,16,47]; one was a population-based cross sectional and comparative study[17]; three were cross-sectional[48-50]; and one a randomized control double-blind crossover trial.[51] Each study identified clusters or patterns of symptom clusters however, each utilized a different number of symptoms in their questionnaires ranging from 14 to 57 symptoms. Finally, of the studies, types of analysis completed were as follows: cluster analysis[8], rank-ordered[3], and the majority of the studies utilized factor analysis.[16-17, 47-51]

The first, a 1986 study by Endicott et al[4], used multiple methods to identify clusters and determine if there were any underlying traits for women with PMS. The study had a population of 64 women that were screened and excluded if they had irregular menstrual cycles, current physical illness, taking medications, on birth control pills, and were not between 18-45 years of age. The authors used a Daily Rating Form to classify women into moderate-to-severe and minimal or no dysphoric premenstrual changes from pre-menses to post-menses. The study utilized different analysis techniques to identify premenstrual changes instead of one all-encompassing premenstrual syndrome term. Using factor analysis, Endicott et al, identified 5 different dimensions of premenstrual change that are possible underlying traits for women with PMS through factor analysis, as shown in Table 1. The 5 dimensions were: (1) physical discomfort, (2) more alcohol, sex, active, (3) low energy, (4) increased consumption, and (5) dysphoric mood. In the second analysis method, cluster analysis, the authors, found that there were 3 clusters that appeared to have the most clinical relevancy. Unlike the factor analysis methods, Endicott et al., does not describe the clusters in detail and only describes the number of individuals in each cluster (N=7, 32, & 25). Cluster analysis and factor analysis results were utilized in the third analysis technique, in which they use a summary scoring system. This system was based on the 5 factor pattern previously described which was corroborated with the cluster analysis results in which they derive patterns of symptom changes. The summary scoring system was then used to test the association between the scores and lifetime diagnosis of major or minor depressive disorder compared to no depressive disorder, in which they did not find significant chi-squared results (4.4, df =0.4). Endicott, et al. used these patterns to describe that instead

of using PMS as an all-encompassing term for severe premenstrual symptoms, it would be better to identify underlying traits to better understand the biological factors, treatment options, and diagnosis. The main limitation to this study was the small size of the study population; which may have limited the ability to fully classify the true underlying factors of the study population. [4]

The second study was a 1995 study by Gotts et al[16], which utilized rank-ordering of symptoms to identify the differences in PMS symptoms and severity within a cycles and define particular unique patterns of experiences. The population in this study included 98 women age 18-45 years of age that had complaints of mood, behavioral, and physical changes 10 days prior to menstruation, complaints abated at or during menstruation followed by a week of no/minimal symptoms, experienced regular menstruation and occurrence of symptoms over the prior 6 cycles, and did not have underlying psychiatric disorders, and did not receive psychotropic medication, psychotherapy or hormone therapy. The participants completed the Moos Menstrual Distress Questionnaire (MDQ) for 2 consecutive cycles. The study used 2 categories of symptoms, psychological and physical symptoms, with the top 4 severe symptoms of concern defining each woman's premenstrual experiences. Example psychological symptoms were: affective (irritability, mood swings); behavioral (crying, yelling); and cognitive (confusion, distractibility). Physical symptoms were: pain-related (headache, sore breasts); and non-pain related (change in appetite, altered motor function). The experiences were ranked by the severity of the symptoms. The authors then used the rank-ordered data to analyze which severe symptoms were most commonly experienced by the women and used the two category data to develop 16 possible premenstrual

experiences. [16] Gotts et al., reported that over 70% of the participants reported their most severe symptom as a psychological problem, which was most commonly reported to be irritability. However, the authors did not list the symptoms or rankings in the journal article and it is not possible to determine the most common or severe and therefore limits the interpretability of this study. The main limitation in this study is the small study population. [16] Additionally, the main purpose of this study was to identify that there were separate and distinct patterns of experiences but not to identify the underlying cause or clusters of symptoms. [16]

In the largest study to date, Woods et al[17], attempted to identify clusters of premenstrual symptoms and the reproducibility of these symptoms versus a comparison population of women that were selected with low-severity symptoms and PMS in 1999. The study used two populations, the first included 345 women in a cross sectional study, aged 18-45 years of age from a northwestern metropolitan city who completed a daily health diary for at least one full menstrual cycle. Inclusion criteria included that they were not currently pregnant, not treated for a gynecological problem, and had menstrual periods. The second sample included 118 women in a comparative study that were between 18-45 years of age. Exclusion criteria were taking oral contraceptives/ other ovarian hormones, antidepressants, tranquilizers, diuretics, hypertension medications, corticosteroids, and were not pregnant or lactating. The women completed the Washington Women's Health Diary (WWHD) which included 57 menstrual symptoms derived from multiple symptom questionnaires including the previously mentioned MDQ. The main result of this study was the identification of 4 main constellations of symptoms derived from factor analysis, which were titled: 1) turmoil, 2) fluid retention,

3) somatic, and 4) arousal symptoms. Unlike the previously described studies by Endicott et al. and Gotts et al., the study by Woods et al., was the one of the only epidemiological studies to provide detailed information on the variance of symptoms that the patterns or groupings for the specific populations in each study described. The authors reported, together the 4 symptom factors accounted for 42% of the variance of symptoms. Individually, turmoil accounted for 23.8% of the variance, fluid retention for 6.8%, somatic for 5.8% and arousal for 5.2%. Four symptoms did not load into any of the four patterns: cramps, hot flashes, sleepiness, and backache. The main limitation of this study was that the daily health diary included information for one menstrual cycle and did not include multiple menstrual cycles. Additionally, current depression status was not taken into consideration which is important when psychological symptoms are assessed during PMS and only factor analysis was completed. [17]

Finally in the remaining five studies [47-51], the study populations ranged from 33 to 423 participants aged 15-48 years and each of these studies utilized factor analysis as the only analysis completed. Similar to Woods et al and Endicott et al, each of the studies identified between 4- and 6-factor patterns [48-51] with the exception of York et al[46], in which 2-factor patterns were extracted, but symptoms were not detailed by York et al. Additionally, the studies that detailed the symptoms in the patterns had emotional and cognitive symptoms loading strongly to the first pattern; many studies reported a water retention pattern and physical patterns in their main results. [16-17, 48-51]

There is an overlap in the symptom clusters that are identified in six of the eight studies [16-17, 48-51], even with different methodologies and symptoms reported. These studies demonstrated that symptoms have common patterns or underlying traits that arise

when looking across studies with different populations, questionnaires, and study designs. However, due to small sample sizes in several of the studies, clearly defined patterns that explain a large amount of variance of the symptoms have not been determined.

We utilized two methods, cluster and factor analysis, to identify premenstrual symptom patterns and examine if the identified patterns hold true for women in the sample population and the sub-population that meet criteria for PMS in two University of Massachusetts studies. The study helps to identify patterns in premenstrual symptoms in women of reproductive age which may aid in the establishment of targeted treatments for premenstrual symptoms. This is particularly important for women that have more severe symptoms that can be debilitating such as those with PMS in which the efficacy of treatments has been shown to be less than 60%. We examined population-based information for women that experience general premenstrual symptoms and women that meet the criteria for PMS as opposed to prior studies that have evaluated only one or the other.

CHAPTER II

STUDY DESIGN AND METHODS

Study Population

We examined premenstrual symptoms for clusters and possible underlying factor patterns using data from two studies of menstrual symptoms conducted at the University of Massachusetts. These studies enrolled a total of 414 young women 18 to 30 years of age from 2006 to 2014. Participants were recruited through advertisements posted around the University of Massachusetts campus in Amherst, MA. All study measurements were completed in one clinic visit which were based on the participant's date of next menstrual period. To confirm the luteal phase time the date of the next menses was subsequently reported. The study questionnaires measured demographics, behavioral, dietary and medical factors including menstrual symptoms and PMS. Eligibility was limited to women currently menstruating and were not pregnant that did not report a history of the following: high blood pressure, elevated cholesterol, kidney or liver disease, bone disease such as osteomalacia, digestive disorders, rheumatologic disease, multiple sclerosis, thyroid disease, hyperparathyroidism, cancer, type 1 or type 2 diabetes, polycystic ovaries, or current use of corticosteroids, anabolic steroids, anticonvulsants, cimetidine, or propranolol.

Assessment of Menstrual Symptoms

Information was collected on current menstrual symptom experiences using a questionnaire based on the Calendar of Premenstrual Experiences (COPE) designed by Mortola et al and is similar to the questionnaire used in the Nurses' Health

Study 2 (NHS2).[2-3,23,25,52] Participants were given a list of 26 behavioral, physical, and affective menstrual symptoms, detailed in Table 1. For each symptom listed, participants were asked if they experienced it "most months of the year, for at least several days before your menstrual period begins", and to rate the usual severity of the symptom.[35] The severity of the individual symptoms was assessed using four categories: none, mild, moderate or severe. Additionally, the women were asked to classify the overall severity of their symptoms as: minimal (no effect on normal activities), mild (noticeable but not troublesome), moderate (interferes with normal activities), or severe (intolerable and prevents activities).

To assess the effect of menstrual symptoms on life activities and interpersonal relationships, the participants were asked if they have experienced relationship discord with a spouse or partner, difficulties parenting, poor work performance/attendance and/or social isolation. For each woman if a positive response to one aspect was indicated, then they were asked to classify the severity of the issue as: 1) not a problem, 2) mild, 3) moderate, or 4) severe. Furthermore, the participant was asked if she had received a clinical diagnosis of PMS.

To determine if the symptoms were associated with other psychiatric conditions that are similar to PMS, women were asked if they had a history of depression, bipolar disorder, or other psychiatric disorders, and if they were currently using anti-depressant medications. The General Depression 20-item Sub-scale of the Inventory of Depression and Anxiety Symptoms (IDAS) was added to the questionnaire in 2008 and was completed by 102 participants and was used to identify women meeting criteria for depression.[35,53] These women were not excluded from study participation or from the full

cohort, but if IDAS score was greater than 50, it was an exclusion criteria for the subset of participants meeting the criteria for PMS. A score greater than 50 suggests a psychiatric disorder that may not yet be diagnosed. The IDAS scores were utilized as a characteristic of the study participants as an additional factor that may be needed for future analyses and the scoring system is detailed elsewhere.[35,53]

In order to identify women who met the criteria for PMS, we identified women meeting the following criteria: (1) experiencing at least one physical and one affective menstrual symptom; (2) symptom severity of "moderate" or "severe", the impact on life activities and relationships of "moderate" or "severe" or at least one symptom rated as "severe"; (3) symptoms being within 14 days to the start of menses; symptoms end within 7 days of the start of menses; (4) symptoms are absent in the week after menses; (5) no evidence of a comorbid psychiatric disorder including IDAS score greater than 50.[23,40,42]

Validity of Methods for Identifying PMS Cases

Validity of our method of identifying PMS case classification made by Bertone-Johnson et al[23] in which direct comparison of the questionnaire method and prospective symptom charting was completed. Forty-one women completed the modified COPE questionnaire in the late-luteal phase of their menstrual cycles. The participants then completed a daily symptom diary utilizing the standard COPE questionnaire for the following cycle. A single blinded observer reviewed the diaries and questionnaires in a random order and categorized the women as meeting the criteria for PMS cases, controls or neither. Bertone-Johnson et al. reported that the sensitivity of the modified

questionnaire compared to the prospective symptom diaries to identify PMS cases was 73%, and the positive predictive value of PMS cases was 80%.[23]

Statistical Analysis

General descriptive statistics of study participants were calculated through the use of summary statistics for age (years), BMI (kg/m^2), age at menarche (years), physical activity (MET/week), IDAS scores, race, Latina ethnicity, education level, current usage of oral contraceptives, smoking status both ever and current usage, marijuana use, current use of anti-depressants, and current use of multivitamins; detailed in Table 2.

Factor analysis techniques were used to identify the possible underlying patterns for all premenstrual symptoms and their severity experienced.[53-54] Exploratory factor analysis was completed in both the full cohort and the subset of participants that met the criteria for PMS independently utilizing the principle components method and procedure FACTOR in SAS.[53-54] To determine the number of factor patterns to extract, three standard methods and criteria were used for both populations: (1) Kaiser-Guttman (K1) rule in which factors with eigenvalues greater than 1.00 are considered, (2) Cattell scree plot in which factors are plotted against eigenvalues in descending order of magnitude are displayed and was used to identify a distinct break in the slope, and (3) parallel analysis (PA) which uses a iterative process to determine if eigenvalues displayed are due to sampling error by comparing random eigenvalues to observed eigenvalues; this aids in extracting patterns that provide meaningful components to extract from the data.[53-54] In the event in which the 3 criteria for extraction do not result in the same number of patterns, extraction pattern values were utilized as a range and the following criteria for

factor loading and pattern retention were utilized to determine the specific number of patterns to retain (e.g. K1 and scree plot identify 4-factor patterns and PA identifies 6-factor pattern; extraction for loading and retention will be performed on 4-, 5-, and 6-factor patterns). The following 3 criteria for factor loading and pattern retention were utilized: (1) symptoms were considered as loading strongly and were retained for loadings >30; (2) a minimum of 3 symptoms were required for each factor pattern to be considered for retention; and (3) if more than 1 symptom loaded strongly to multiple factors the factor with the highest loading was retained. [53-54] Any symptoms not loading strongly to any of the factor patterns were removed from further analysis. To aid in the interpretability of factor patterns, Varimax rotation of symptoms was utilized and factor scores were provided for each of the symptom which was consistent with prior literature [7,16-17,47-51,53-54] (Tables 3-5). After factor patterns were extracted and identified, reliability tests were completed for each factor utilizing Cronbach's alpha[53-54] (Tables 6 and 7). Additionally demographic and cohort characteristic were provided for each of the factor pattern and were stratified by score quartiles. Continuous demographic variables were compared between factor patterns by ANOVA tests and categorical variables were compared using Chi-square or Fisher's exact tests in both the full cohort and subset (Tables 8 and 9).

Additionally, linear relations between factor patterns and BMI, total energy-adjusted folate and total energy-adjusted niacin were assessed, with results shown as Pearson correlation coefficients presented in Tables 10 and 11.

Non-hierarchical cluster analysis was used to group individuals into subgroups, otherwise known as clusters. [54-55] The groups of individuals cluster by having experienced

similar symptoms and similar severity of these symptoms. Unlike factor analysis, each woman may only belong to one cluster. The clusters were identified by utilizing the data provided by each woman regarding the symptoms and severity experienced using k-means and the procedure FASTCLUS in SAS. [54-55] The number of clusters was determined through a stepdown method starting with 20 clusters to the final 4 clusters. To retain a particular amount of clusters in each run, each cluster needed to have a minimum of 3 participants to ensure there were not too many clusters for interpretation of the results. Tables 12 and 13 demonstrate the demographic and cohort characteristics for each of the clusters in both the full cohort and subset. ANOVA tests were completed for each of the continuous demographic variables and Chi-square or Fisher's exact tests were completed for each of the categorical variables. Table 14 and 15 demonstrate the mean scores for each factor pattern along with ANOVA tests. In addition Figures 15-22 display the distribution of factor values for the participants in each of the clusters in both the total study population and in the subset meeting criteria for PMS.

All analyses were completed using SAS Version 9.4.

CHAPTER III

RESULTS

General Information

The demographic characteristics of all study participants (n=414) and the subset of the women who meet the criteria for PMS (n=80) are displayed in Table 1. The mean age of the participants in the total population was 21.0 years and in the subset 20.9 years. The majority of study participants reported white race (82.3%) with a small proportion reporting Hispanic ethnicity (6.8%). Study participants meeting criteria for PMS reported slightly higher use of oral contraceptives, being ever/current smokers, and smoking marijuana. The premenstrual symptoms reported by all study participants are displayed in Figure 1 and the subset of women meeting criteria for PMS in Figure 2.

Factor Analysis

As discussed above, exploratory factor analysis (EFA) was completed in both the full cohort and subset independently. In the full cohort, all 3 methods and criteria suggested that a 4-factor pattern was to be extracted, as displayed in Figure 3. Utilizing the procedure FACTOR and the aforementioned Varimax rotation, symptoms were given factor loading scores to reflect their contribution to each of the 4-factor patterns. Of the 26 symptoms reported, 2 symptoms (hot flashes and swelling of extremities) did not load strongly (i.e. loading >30) on any of the factor pattern and therefore were removed from subsequent analysis. Upon removal, variance for the factors was reviewed again, and found not to have been affected by the removal of these symptoms and therefore 24

symptoms remained. Factor loading and rotation was completed again for these 24 symptoms only. Factor loadings and scores are reported in Table 4 and 5.

In the subset of women meeting criteria for PMS, the 3 extraction methods and criteria had differing results. K1 demonstrated 8 factors with eigenvalue >1; the scree plot displayed a break in slope at 4 and 6 factors, and PA demonstrated 6 factors results are displayed in Figure 4. It was determined that 8-factor patterns would be a viable starting point for factor analysis and Varimax rotation. Under the 8-, 7-, and 6-factor patterns, 2 symptoms (hot flashes and swelling of extremities) did not load strongly (>30) and were removed from subsequent analysis (as occurred in the full cohort analysis). After removal of the 2 symptoms, factor loading and rotation was completed for the remaining 24 symptoms. In the 8- and 7-factor patterns, only factors 1-4 met the factor loading and retention criteria and were therefore dismissed. In the 6-factor pattern, factors 5 and 6 did not meet the criteria for having at least 3 symptoms loading strongly. The above process was repeated for a 5-factor pattern (Table 4) and a 4 factor pattern (Table 5). Under both patterns all 3 of the factor loading and pattern criteria were met.

Factor patterns were named in a descriptive manner for the overall interpretation and comparability with previous studies. An example is, if a pattern has mood swings, emotional hypersensitivity, and tendency to cry easily; a pattern name of "emotional" would describe the overall symptoms experienced in this pattern.

To determine which factor pattern would be retained for the PMS subset, reliability and interpretability of the factors were considered. Reliability tests were completed for the 3 factor patterns retained, 4-factor full cohort pattern and the 5- and 4-

factor pattern in the subset. Cronbach's alpha (α) was utilized to reviewing the average correlation of the set of the symptoms in each pattern. For this metric, $\alpha<0.60$ is considered poor, $0.60\leq\alpha<0.70$ is considered acceptable, $0.70\leq \alpha<0.80$ is considered good, and $\alpha\geq0.90$ is considered excellent. [53-54] Table 6 displays the 4-factor pattern for all participants along with symptoms and factor loading scores for each symptom. All patterns were observed to have reliability estimates in the good to excellent range: Emotional ($\alpha=0.90$), Psychological ($\alpha=0.83$), Physical ($\alpha=0.74$) and Consumption ($\alpha=0.71$). Table 7 displays the 5-factor pattern for women meeting criteria for PMS and Table 8 displays the 4-factor pattern for this subset. In the 5-factor pattern alpha levels were considered poor in the General Physical Pattern and averaged lower than the levels in the 4-factor pattern, additionally, the 4-factor pattern also provides better interpretability of the factors. We thus opted to retain the 4-factor pattern for further analysis.

The 4-factor patterns identified in the full cohort were similar in symptoms experienced to those of the PMS subset, with the exception of fatigue, abdominal bloating, headache, and dizziness. The remaining 20 symptoms loaded into the same symptom patterns in both the total population and PMS subset. These 4 patterns explained 58.4% of the variance in the full cohort and 48.6% in the PMS subset. For each pattern, women were classified into quartile based on factor scores. We then evaluated how demographic and behavioral characteristics varied by factor scores (Tables 9 and 10). Table 9 shows the characteristics participants in the full cohort by quartile of each of the four symptom patterns. IDAS Score (p-value <0.001) and current multivitamin usage ($p=0.02$) varied statistically significant between quartiles of Emotional pattern. The

Psychological symptom pattern, was associated with IDAS Score ($p < 0.001$) and reporting white race ($p = 0.02$). Only reporting white race ($p = 0.01$) was significantly associated with quartile of the factor corresponding to physical symptoms. Finally, BMI ($p = 0.01$), physical activity ($p = 0.02$), IDAS score ($p < 0.001$), and ever having smoked ($p = 0.03$) were significantly related to levels of the consumption pattern. Table 10 displays the above described comparison of characteristics by quartiles of the four symptom patterns by restricted to the subset of those who met the criteria for PMS. In these comparisons, associations were observed between the Emotional pattern and college was significant ($p = 0.05$); Psychological pattern, and IDAS score ($p = 0.002$); Physical pattern and physical activity ($p = 0.04$) and IDAS score ($p=0.02$); and finally, between Consumption pattern reporting white race ($p = 0.02$).

Factor Analysis with BMI, total folate and total niacin correlations

Table 11 demonstrates correlation coefficients of the factor scores for each of the 4-factor with BMI, total energy-adjusted folate, and total energy-adjusted niacin 3 factors previously observed to be associated with prevalence of PMS in this population. In the full cohort, BMI was significantly associated with factor scores for Consumption (0.11, $p=0.03$), but not other factors. Niacin intake was marginally associated with Consumption score as well. Folate intake was not correlated with factor score for any of the 4 patterns. Table 12 demonstrates correlation coefficients in the subset, in which BMI was significantly associated with the factor scores for Consumption (0.22, $p=0.05$).

Cluster Analysis

As discussed above, cluster analysis (CA) was completed in both the full cohort and the subset independently. The FASTCLUS procedure was used to perform non-hierarchical CA on both the full cohort and subset to determine membership for each cluster for a set number of clusters. Upon analysis of clusters identified, those with fewer than 3 people were removed. Four clusters were retained for both the full cohort and the PMS subset. Figures 5 and 6 graphically display the distribution of participants in both the full cohort and the PMS subset, respectively. Figures 7-10 display the distribution of symptoms and severity of symptoms reported by all participants in each of the 4 clusters. Figures 11-14 display the distribution of symptoms and severity reported by the PMS subset in each of the final 4 clusters.

In the full cohort, Cluster 1 (n=187), Cluster 2 (n=75), Cluster 3 (n=102), and Cluster 4 (n=50) were identified; Table 13 shows the characteristics of women in each of these four clusters. Mean age at menarche ($p=0.02$), IDAS score ($p<0.001$), and white race significantly ($p<0.001$), differed across clusters and current anti-depressant use was significant ($p =0.05$) higher in Cluster 4 than in the other 3 clusters.

Table 14 displays characteristics in the PMS subset, Cluster 1 (n=30), Cluster 2 (n=7), Cluster 3 (n=23), and Cluster 4 (n=20). When comparison characteristics of women across clusters, ever having smoked was found to be significantly different ($p=0.03$) while differences in IDAS score were marginally higher in Cluster 3 than Cluster 1 ($p=0.07$).

Table 15 displays the mean factor pattern scores and standard deviation of all participants based on cluster. When the patterns were compared across clusters, each

pattern was found to be significantly different for each of the four factor patterns ($p<0.001$). Table 16 displays mean factor scores and standard deviation of participants meeting the criteria for PMS based on cluster. As with the total study population, each pattern was found to be significantly different for each of the four factor patterns ($p<0.001$).

In Figures 15-18 the distribution of factor scores is for each cluster is displayed in boxplots. The distribution of Factor 1 displays Clusters 2 and 4 with higher overall mean scores than in Clusters 1 and 3. Factor 2 displays Cluster 4 having higher overall scores than in the other clusters. In Figures 19-22 the distribution of factor scores varies between all of the clusters.

CHAPTER IV

DISCUSSION

In our study, four factor patterns emerged in the full cohort of women and in the PMS subset. We identified 4 symptom patterns in both the full cohort and the PMS subset. Based on the factor loadings of the individual symptoms used for analysis, we labeled these symptom patterns as Emotional, Psychological, Physical and Consumption. The symptoms that contributed the highest loading scores in each of the four symptoms were similar to symptom patterns reported in prior studies. [4,16-17, 47-51] As in prior epidemiological studies, the symptoms that loaded strongly onto the Emotional pattern and the Psychological pattern had the strongest loadings of the 4 factors and the highest reliability scores of the four patterns (Emotional α=0.9 in the total study population and 0.8in the subset); Psychological (α=0.83 in the total study population and 0.78 in the subset). Additionally, the symptoms that loaded into the Physical pattern also tend to cluster together across many of the studies. [4, 16-17, 47-51]

Our results were relatively consistent with the previous studies by Endicott et al, Woods et al, Siegel et al, Alivir et al, and Chaturvedi et al. Many of these studies had cohorts of women across the United States[4, 16-17, 47-49, 51] and one study in India[50], and included women from the general population and those that met the criteria for PMS.

One major difference in the factor pattern results between our study and previous analyses was the Consumption pattern. While this was similar to the factor patterns found by Endicott et al and Alivir et al, it was not identified in other studies. First, the existing studies have differed substantially regarding the specific menstrual symptoms

assessed on study questionnaires and the total number of symptoms provided to participants (ranging from 14-57 distinct symptoms). Other factors that might also contribute to the differences can include the other treatments; oral contraceptive usage of participants varied among prior studies, many of which studies did not have the same exemption criteria for participants. [16-17, 48-51]

Overall, the patterns we identified seem to be generally consistent with other studies in both clinical and non-clinically presenting participants. However, the symptoms hot flashes and swelling of the extremities did not load into any of our factor patterns, unlike in three of the previous studies.[17,49-50] These studies only included one of the two symptoms on the questionnaires but not both. In the studies by Woods et al and Chaturvedi et al swelling of the extremities fell into the fluid retention categories with breast pain/engorgement and weight gain, bloating, acne, and increased sexual desire. [17,51] Additionally, hot flashes was only included in one other study, Siegel et al, in which it was retained in the physical discomfort pattern with other symptoms like cramps, backache, nausea, and dizziness/fainting.[48] Due to differences in questionnaire and cohort characteristics further research is needed.

Finally, an interesting piece, is that in each study between 4 and 6 patterns were extracted from the data gathered from individuals in the general population studies and also in studies that focused primarily on women that met the criteria for PMS. [16-17,48-49,51] This may provide further evidence that the general patterns of symptoms may indeed have a latent or physiologic construct and may not be just a random occurrence.

In addition to the EFA the 4 factors derived were utilized to test the correlations between known risk factors. BMI was found to have a weak but statistically significant relation with the Consumption pattern score. Consideration of how risk factors are correlated with symptom patterns of in more depth, to see which symptoms are related, illustrates the potential benefit of factor analysis for the development of interventions.

When we utilized cluster analysis techniques to determine constellations of women, four clusters were identified in the full cohort and also in the PMS subset. Unlike the factor patterns that were derived, the results from the cluster analysis provided were difficult to interpret. For example, in the full cohort the women that were clustered into Cluster 1 tended to either have no symptoms or mild symptoms reported, but Cluster 3 tended to report mild to moderate Physical and Emotional symptoms. Additionally, in the PMS clusters, Cluster 1 participants were most likely to report mild to moderate Physical and Emotional symptoms and Cluster 2-4 were likely to report moderate or severe Physical, Emotional, Cognitive, and Psychological symptoms. Upon further analysis, IDAS score was statistically significant when comparing the women across the different clusters in both the full cohort and PMS subset. White race, age at menarche, use of anti-depressants, and ever having smoked were found to be significant in either the full cohort or the PMS subset but not in both. The comparison of clusters and mean factor scores was helpful in understanding that there were differences between the clusters and the overall symptom patterns experienced however; further analysis of additional characteristics might be needed to fully understand the potential utility of the clusters.

The main limitations of factor analysis are that there are several decisions that are made in the process that are arbitrary but still important, and patterns derived can vary due to population characteristics. Some of the decisions made include determining the number of factors to extract, the method of rotation chosen, and the labelling of the new patterns with the number of factors to extract and the method of rotation chosen being of the highest consequence. If we chose too many or too few factors, the symptoms loading could be impacted, which could limit the insights into underlying patterns. In order to minimize the effect that these two decisions have on the findings, we utilized several known and well established methods of extracting patterns in order to make this decision. These 3 methods provided similar numbers of patterns to extract, which were also in agreement with the prior literature. Finally the patterns derived can vary due to other characteristics of the study population such as age and diet. While this may be an issue, our study findings are consistent with those from studies with very different populations, including participant ages varying between 15-48 years of age, well beyond the ages of our study, and from cohorts around the U.S. and one in India. [4, 16-17, 47-51] These observations suggest that these are fairly consistent symptom patterns experienced in multiple populations and when measured by many different tools.

The main limitations of cluster analysis are similar to that of factor analysis in that he clusters are dependent on the participant characteristics and can vary due to specific demographics like age or socioeconomic status. Additionally, cluster analysis will always provide mutually-exclusive groupings of participants. Unfortunately due to lack of studies using cluster analysis it is difficult to determine if the clusters in this study are similar to other studies with similar participant characteristics.[4] Further research is

needed to determine if these clusters are meaningful or if they are specific to this one population.

General study limitations include non-differential misclassification of the symptoms and generalizability. In this study a non-differential misclassification of the symptoms can occur at two points. First the information gathered on the symptoms was provided cross-sectionally and the women were asked to recall the symptoms, frequency, and severity. Although this would directly impact our symptom patterns, the questionnaire utilized has been previously validated and found to have fairly high sensitivity. [23] Secondly, there are over 100 possible distinct symptoms that women may experience and our questionnaire was limited to 26. [23] However, the questionnaire used has been derived from open-ended symptom diaries and reflects the most common and important symptoms from these diaries. Therefore, these two issues of non-differential misclassification of the symptoms are likely to be minimal in magnitude and of little consequence to the results.

Finally, the generalizability of our study may also be a limitation; our study population is fairly homogenous with a majority of the women reporting white race and between ages 20 and 22. There may be some physiologic differences in women that are substantially younger or older with either different symptom patterns or etiologic factors affecting these age groups. However, as previously mentioned, the results from factor analysis patterns have been fairly consistent across studies, study populations, and use of multiple measurement tools.

CHAPTER V

CONCLUSION

In conclusion, the factor analysis patterns that were identified in this study provide interesting results that have been fairly consistent from study to study. These results suggest that there are between four and six symptom patterns that are routinely extracted with similar constellations of symptoms in these patterns. Further research is needed to provide detailed information on whether these patterns are anomalies or if they are driven by specific etiologies. Preferably this research would performed in a heterogeneous population spanning all ages of reproductive women using one measurement tool. Additionally, this information may be useful in understanding how different risk factors are correlated with these patterns to better understand the etiology of these symptoms.

Table 1. Symptoms Included in Questionnaire , UMASS Vitamin D Study and PMS Study (2006-2014)

Abdominal bloating	Food cravings	Insomnia
Breast tenderness	Palpitations	Angry outbursts
Dizziness	Anxiety/Nervousness	Desire to be alone
Headache	Increased/Decreased Appetite	Depression
Hot flashes	Irritability	Confusion
Nausea	Emotional hypersensitivity	Forgetfulness
Swelling in Extremities	Fatigue	Abdominal cramping
Acne	Mood swings	Lower back pain
Diarrhea/Constipation	Tendency to cry easily	

Table 2. Characteristics of All Study Participants (n= 414) and Subset Participants Meeting Criteria for Premenstrual Syndrome (PMS) (n=80), UMASS Vitamin D Study and PMS Study (2006-2014)

		All Participants	Subset.: Meeting PMS Criteria
Characteristics		**Mean (SD)**	**Mean (SD)**
Age (years)		21.0 (2.6)	20.9 (2.5)
BMI (kg/m^2)		23.1 (3.4)	22.9 (3.3)
Age at menarche (years)		12.5 (1.4)	12.2 (1.4)
Physical activity (MET/week)		54.0 (50.4)	46.6 (41.6)
IDAS Score (n=202)		37.0 (10.2)	39.4 (10.7)
		N (%)	**N (%)**
Race (n=413)	: White	340 (82.3)	59 (73.8)
	: Black	9 (2.2)	3 (3.8)
	: Other	64 (15.5)	18 (22.5)
Hispanic		28 (6.8)	7 (8.8)
Education: Some /Cur. College		354 (85.5)	70 (87.5)
Currently using OC		186 (44.9)	42 (52.5)
Smoking	: Ever	46 (11.1)	14 (17.5)
	: Current	19 (4.6)	7 (8.9)
	: Marijuana (n=412)	121 (29.4)	27 (33.8)
Currently using Anti-Depressants [a]		24 (5.8)	0 (0.0)
Currently taking Multivitamins (n=412)		167 (40.5)	29 (37.2)

[a] Current usage of anti-depressants is an exclusion criteria for the sub-population of meeting criteria for PMS.

Table 3. All Participants (n=414) 4-Factor Pattern Varimax Rotated with Factor Scores Multiplied by 100 for 24 Symptoms, UMASS Vitamin D Study and PMS Study (2006-2014)

Symptom	Factor 1 (Emotional)	Factor 2 (Psychological)	Factor 3 (Physical)	Factor 4 (Consumption)
Emotional Hypersensitivity	***84***	16	18	25
Tendency to Cry Easily	***81***	11	26	20
Mood Swings	***77***	31 *	16	22
Irritability	***72***	30 *	18	25
Angry Outbursts	***68***	42 *	6	-1
Anxiety/ Nervousness	30 *	***71***	3	30 *
Depression	45 *	***60***	6	9
Desire to be Alone	43 *	***54***	13	21
Confusion	13	***51***	3	17
Headache	10	***50***	32 *	5
Forgetfulness	8	***50***	7	17
Insomnia	12	***49***	16	16
Fatigue	25	***47***	35 *	35 *
Dizziness	9	***38***	27	-7
Palpitations	8	***32***	14	9
Lower Back Pain	6	20	***78***	11
Abdominal Cramping	19	13	***77***	0
Diarrhea/ Constipation	14	45 *	***48***	9
Breast Tenderness	35 *	-12	***48***	16
Abdominal Bloating	15	17	***47***	40 *
Nausea	6	32 *	***45*** *	5
Food Cravings	32 *	16	19	***81***
Increased/Decreased Appetite	26	23	21	***78***
Acne	10	27	-7	***50***

Note: 2 symptoms did not load onto any factor pattern and were removed: Hot flashes and Swelling of Extremities.

* Indicates that this symptom also loaded strongly on another factor. Highest loading factor was kept.

Table 4. Subset of Participants Meeting Criteria for PMS (n=80) 5-Factor Pattern Varimax Rotated with Factor Scores Multiplied by 100 for 24 Symptoms, UMASS Vitamin D Study and PMS Study (2006-2014)

Symptom	Factor 1 (Psychological)		Factor 2 (Emotional)		Factor 3 (Consumption)	Factor 4 (GI Physical)	Factor 5 (General Physical)	
Depression	***68***		43	*	-7	-4	4	
Anxiety/ Nervousness	***65***		18		18	-9	-5	
Insomnia	***65***		-5		21	6	24	
Desire to be Alone	***62***		14		12	13	-9	
Confusion	***54***		-7		0	4	28	
Forgetfulness	***49***		6		19	4	41	*
Palpitations	***36***		6		15	11	23	
Emotional Hypersensitivity	2		***81***		10	0	2	
Mood Swings	16		***79***		9	-11	2	
Irritability	21		***71***		24	3	2	
Angry Outbursts	53	*	***63***		-10	-7	8	
Tendency to Cry Easily	-7		***59***		1	15	26	
Food Cravings	-7		30	*	***84***	-3	-8	
Increased/Decreased Appetite	7		21		***82***	8	-2	
Fatigue	37	*	-6		***51***	14	20	
Acne	34	*	4		***51***	-23	1	
Abdominal Bloating	17		-9		***41***	21	14	
Diarrhea/ Constipation	36	*	18		6	***73***	-22	
Abdominal Cramping	-12		2		5	***70***	20	
Lower Back Pain	-4		2		18	***67***	43	*
Nausea	7		-8		-3	***51***	10	
Headache	30	*	-2		3	11	***76***	
Breast Tenderness	-2		25		6	16	***63***	
Dizziness	32	*	15		-10	28	***45***	

Note: 2 symptoms did not load onto any factor pattern and were removed: Hot flashes and Swelling of Extremities.

* Indicates that this symptom also loaded strongly on another factor. Highest loading factor was kept.

Table 5. Subset of Participants Meeting Criteria for PMS (n=80) 4-Factor Pattern Varimax Rotated with Factor Scores Multiplied by 100 for 24 Symptoms, UMASS Vitamin D Study and PMS Study (2006-2014)

Symptom	Factor 1 (Psychological)		Factor 2 (Emotional)		Factor 3 (Physical)	Factor 4 (Consumption)
Insomnia	***68***		-4		14	18
Depression	***66***		44	*	-6	-6
Anxiety/ Nervousness	***63***		19		-15	19
Desire to be Alone	***59***		14		1	14
Confusion	***58***		-5		14	-3
Forgetfulness	***56***		8		23	14
Palpitations	***39***		7		19	13
Emotional Hypersensitivity	0		***80***		3	12
Mood Swings	14		***80***		-7	10
Irritability	20		***71***		4	26
Angry Outbursts	52	*	***64***		-5	-9
Tendency to Cry Easily	-4		***59***		29	0
Lower Back Pain	2		0		***80***	16
Abdominal Cramping	-10		-1		***70***	7
Breast Tenderness	8		26		***50***	-1
Headache	43	*	1		***49***	-6
Nausea	8		-10		***47***	-1
Dizziness	38	*	16		***45***	-14
Diarrhea/Constipation	30	*	14		***45***	13
Food Cravings	-7		28		-4	***85***
Increased/Decreased Appetite	8		20		8	***82***
Acne	35	*	5		-20	***49***
Fatigue	41	*	-6		21	***48***
Abdominal Bloating	20		-10		24	***40***

Note: 2 symptoms did not load onto any factor pattern and were removed: Hot flashes and Swelling of Extremities.

* Indicates that this symptom also loaded strongly on another factor. Highest loading factor was kept.

Table 6. All Participants (n=414) Varimax Rotated 4-Factor Patterns and Labels with Reliability Coefficients (Cronbach's Alpha) for 26 Symptoms, UMASS Vitamin D Study and PMS Study (2006-2014)

Emotional Pattern Cronbach's Alpha = 0.90		***Psychological Pattern*** Cronbach's Alpha = 0.83		***Physical Pattern*** Cronbach's Alpha = 0.74		***Consumption Pattern*** Cronbach's Alpha = 0.71		***Non-Loading Symptoms***
Symptoms	**Score**	**Symptoms**	**Score**	**Symptoms**	**Score**	**Symptoms**	**Score**	**Symptoms**
Emotional Hypersensitivity	**84**	Anxiety/ Nervousness	**71**	Lower Back Pain	**78**	Food Cravings	**81**	Hot Flashes
Tendency to Cry Easily	**81**	Depression	**60**	Abdominal Cramping	**77**	Inc./Dec. Appetite	**78**	Swelling in Extremities
Mood Swings	**77**	Desire to be Alone	**54**	Diarrhea/ Constipation	**48**	Acne	**50**	
Irritability	**72**	Confusion	**51**	Breast Tenderness	**48**			
Angry Outbursts	**68**	Headache	**50**	Abdominal Bloating	**47**			
		Forgetfulness	**50**	Nausea	**45**			
		Insomnia	**49**					
		Fatigue	**47**					
		Dizziness	**38**					
		Palpitations	**32**					

Table 7. Subset of Participants Meeting Criteria for PMS (n=80) Varimax Rotated 5-Factor Patterns and Labels with Reliability Coefficients (Cronbach's

Emotional Pattern Cronbach's Alpha= 0.80		***Psychological Pattern*** Cronbach's Alpha= 0.78		***GI Physical Pattern*** Cronbach's Alpha= 0.63		***Consumption Pattern*** Cronbach's Alpha= 0.69		***General Physical Pattern*** Cronbach's Alpha= 0.59	
Symptoms	**Score**	**Symptoms**	**Score**	**Symptoms**	**Score**	**Symptoms**	**Score**		
Emotional Hypersensitivity	***81***	Depression	***68***	Diarrhea/ Constipation	***73***	Food Cravings	***84***	Headache	***76***
Mood Swings	***79***	Anxiety/ Nervousness	***65***	Abdominal Cramping	***70***	Increased/Decreased Appe	***82***	Breast Tenderness	***63***
Irritability	***71***	Insomnia	***65***	Lower Back Pain	***67***	Fatigue	***51***	Dizziness	***45***
Angry Outbursts	***63***	Desire to be Alone	***62***	Nausea	***51***	Acne	***51***		
Tendency to Cry Easily	***59***	Confusion	***54***			Abdominal Bloating	***41***	***Non-Loading Symptoms***	
		Forgetfulness	***49***					**Symptoms**	
		Palpitations	***36***					Hot Flashes	
								Swelling in Extremities	

Table 8. Subset of Participants Meeting Criteria for PMS (n=80) Varimax Rotated 4-Factor Patterns and Labels with Reliability Coefficients (Cronbach's Alpha) for 26 Symptoms, UMASS Vitamin D Study and PMS Study (2006-2014)

Emotional Pattern Cronbach's Alpha = 0.80		***Psychological Pattern*** Cronbach's Alpha = 0.78		***Physical Pattern*** Cronbach's Alpha = 0.70		***Consumption Pattern*** Cronbach's Alpha = 0.69		***Non-Loading Symptoms***
Symptoms	**Score**	**Symptoms**	**Score**	**Symptoms**	**Score**	**Symptoms**	**Score**	**Symptoms**
Emotional Hypersensitivity	**80**	Insomnia	**68**	Lower Back Pain	**80**	Food Cravings	**85**	Hot Flashes
Mood Swings	**80**	Depression	**66**	Abdominal Cramping	**70**	Inc./Dec. Appetite	**82**	Swelling in Extremities
Irritability	**71**	Anxiety/ Nervousness	**63**	Breast Tenderness	**50**	Acne	**49**	
Angry Outbursts	**64**	Desire to be Alone	**59**	Headache	**49**	Fatigue	**48**	
Tendency to Cry Easily	**59**	Confusion	**58**	Nausea	**47**	Abdominal Bloating	**40**	
		Forgetfulness	**56**	Dizziness	**45**			
		Palpitations	**39**	Diarrhea/Constipation	**45**			

Table 9. Characteristics of All Study Participants (n=414) Based on Varimax Rotated 4-Factor Patterns, UMASS Vitamin D Study and PMS Study (2006-2014)

	Emotional Pattern					Psychological Pattern					Physical Pattern					Consumption Pattern				
	Q1		Q4			Q1		Q4			Q1		Q4			Q1		Q4		
	Mean	**SD**	**Mean**	**SD**	**p-value ***	**Mean**	**SD**	**Mean**	**SD**	**p-value ***	**Mean**	**SD**	**Mean**	**SD**	**p-value ***	**Mean**	**SD**	**Mean**	**SD**	**p-value ***
Age (years)	21.0	2.9	21.1	2.5	0.96	21.0	2.1	21.1	2.7	0.72	20.8	2.4	21.1	2.7	0.55	20.9	2.3	21.5	2.8	*0.07*
BMI (kg/m^2)	23.0	3.5	22.9	3.3	0.71	23.4	3.3	23.4	3.0	0.77	23.0	3.2	23.4	3.9	0.34	22.6	3.5	23.7	3.6	**0.01**
Age at menarche (years)	12.5	1.6	12.3	1.4	0.23	12.6	1.4	12.3	1.4	0.17	12.5	1.5	12.2	1.7	0.10	12.5	1.4	12.4	1.5	0.48
Physical activity (MET/wk)	49.1	43.5	57.8	55.5	0.19	62.1	56.5	50.5	52.9	0.29	57.6	54.7	43.7	38.6	*0.06*	46.3	47.3	65.5	49.3	**0.02**
IDAS Score	34.3	8.5	41.9	11.4	**<0.001**	34.2	7.2	42.3	11.4	**<0.001**	37.0	11.1	39.6	11.1	0.13	36.5	11.6	39.1	9.6	**<0.001**
	N	**%**	**N**	**%**	**p-value ***	**N**	**%**	**N**	**%**	**p-value ***	**N**	**%**	**N**	**%**	**p-value ***	**N**	**%**	**N**	**%**	**p-value ***
Race : White	85	83%	83	80%	0.74	88	85%	75	72%	**0.02**	78	75%	80	78%	**0.01**	84	81%	80	78%	0.31
Hispanic	7	7%	7	7%	0.96	3	3%	9	9%	0.31	11	11%	8	8%	0.16	8	8%	6	6%	0.69
Education: Some/Cur. College	90	87%	91	88%	0.70	85	83%	90	87%	0.65	92	88%	93	90%	*0.09*	88	85%	84	82%	0.50
Currently using OC	45	44%	53	51%	0.41	47	46%	48	46%	0.94	45	43%	46	45%	0.94	49	47%	40	39%	0.28
Smoking : Ever	6	6%	16	15%	0.16	12	12%	10	10%	0.96	13	13%	11	11%	0.97	10	10%	19	18%	**0.03**
: Current	3	3%	5	5%	0.59	4	4%	6	6%	0.73	6	6%	4	4%	0.93	5	5%	6	6%	0.83
: Marijuana	31	30%	24	23%	0.17	27	26%	32	31%	0.83	32	31%	33	32%	0.78	23	22%	32	31%	0.31
Current use Anti-Depressants	7	7%	5	5%	0.87	4	4%	9	9%	0.49	7	7%	8	8%	0.62	5	5%	10	10%	0.11
Current use Multivitamins	43	42%	28	27%	**0.02**	32	31%	39	38%	*0.07*	38	37%	35	34%	0.24	39	38%	43	42%	0.93

Note: Q2 and Q3 for all factors were removed to save space in the table.

* P-values calculated for continuous variables using ANOVA and for categorical variables using Chi Square. Fisher's Exact Test used due to low (<5) expected cell counts.

Table 10. Characteristics of Participants Meeting Criteria for PMS (n=80) Based on Varimax Rotated 4-Factor Patterns, UMASS Vitamin D Study and PMS Study (2006-2014)

	Emotional Pattern					Psychological Pattern					Physical Pattern					Consumption Pattern				
	Q1		Q4			Q1		Q4			Q1		Q4			Q1		Q4		
	Mean	**SD**	**Mean**	**SD**	**p-value ***	**Mean**	**SD**	**Mean**	**SD**	**p-value ***	**Mean**	**SD**	**Mean**	**SD**	**p-value ***	**Mean**	**SD**	**Mean**	**SD**	**p-value ***
Age (years)	21.0	2.1	21.1	2.7	0.47	21.0	2.9	21.1	2.5	0.96	20.8	2.4	21.1	2.7	0.77	20.9	2.3	21.5	2.8	0.63
BMI (kg/m^2)	23.4	3.3	23.4	3.0	0.61	23.0	3.5	22.9	3.3	0.89	23.0	3.2	23.4	3.9	0.97	22.6	3.5	23.7	3.6	*0.09*
Age at menarche (years)	12.6	1.4	12.3	1.4	0.36	12.5	1.6	12.3	1.4	0.74	12.5	1.5	12.2	1.7	0.17	12.5	1.4	12.4	1.5	0.32
Physical activity (MET/wk)	62.1	56.5	50.5	52.9	0.82	49.1	43.5	57.8	55.5	0.66	57.6	54.7	43.7	38.6	**0.04**	46.3	47.3	65.5	49.3	0.55
IDAS Score	34.2	7.2	42.3	11.4	0.99	34.3	8.5	41.9	11.4	**0.002**	37.0	11.1	39.6	11.1	**0.02**	36.5	11.6	39.1	9.6	0.90
	N	**%**	**N**	**%**	**p-value ***	**N**	**%**	**N**	**%**	**p-value ***	**N**	**%**	**N**	**%**	**p-value ***	**N**	**%**	**N**	**%**	**p-value ***
Race : White	12	60%	15	75%	0.43	15	75%	13	65%	0.75	13	65%	13	65%	*0.09*	14	70%	10	50%	**0.02**
Hispanic	3	15%	2	10%	0.83	1	5%	1	5%	0.83	1	5%	3	15%	0.83	1	5%	4	20%	0.20
Education: Some/Cur. College	14	70%	19	95%	**0.05**	17	85%	17	85%	0.65	19	95%	19	95%	0.17	19	95%	17	85%	0.71
Currently using OC	9	45%	14	70%	0.33	10	50%	9	45%	0.61	10	50%	10	50%	0.90	13	65%	8	40%	0.33
Smoking : Ever	5	25%	1	5%	0.39	5	25%	1	5%	0.28	4	20%	2	10%	0.82	4	20%	4	20%	0.39
: Current	1	5%	1	5%	*0.06*	1	5%	2	10%	0.66	3	15%	1	5%	0.83	1	5%	2	10%	0.56
: Marijuana	7	35%	5	25%	0.65	6	30%	8	40%	0.35	7	35%	4	20%	0.10	6	30%	5	25%	0.35
Current use Anti-Depressants [a]		-		-	-		-		-	-		-		-	-		-		-	-
Current use Multivitamins	11	55%	4	20%	0.16	5	25%	7	35%	0.52	6	30%	5	25%	0.35	7	35%	8	40%	0.96

Note: Q2 and Q3 for all factors were removed to save space in the table.

[a] Current usage of anti-depressants is an exclusion criteria for the sub-population of meeting criteria for PMS.

* P-values calculated for continuous variables using ANOVA and for categorical variables using Chi Square. Fisher's Exact Test used due to low (<5) expected cell counts.

Table 11: Pearson Correlation Coefficients in All Study Participants (n=414) Based on the 4-Factor Pattern, UMASS Vitamin D Study and PMS Study (2006-2014)

	Emotional	p-value	Psychological	p-value	Physical	p-value	Consumption	p-value
BMI	-0.02	0.69	0.01	0.88	0.04	0.36	**0.11**	**0.02**
Total Niacin	-0.06	0.22	-0.05	0.27	0.00	0.92	*0.09*	*0.06*
Total Folate	-0.06	0.19	-0.01	0.77	-0.05	0.27	0.06	0.22

Table 12: Pearson Correlation Coefficients in Participants Meeting Criteria for PMS (n=80) Based on the 4-Factor Pattern, UMASS Vitamin D Study and PMS Study (2006-2014)

	Emotional	p-value	Psychological	p-value	Physical	p-value	Consumption	p-value
BMI	0.02	0.88	-0.02	0.89	0.00	0.99	**0.22**	**0.05**
Total Niacin	-0.05	0.67	-0.02	0.90	-0.05	0.68	-0.05	0.69
Total Folate	-0.13	0.27	-0.04	0.75	0.03	0.77	0.05	0.67

Table 13. Characteristics of All Study Participants (n=414) Based on Cluster Analysis, UMASS Vitamin D Study and PMS Study (2006-2014)

	Cluster 1 n= 187		Cluster 2 n= 75		Cluster 3 n= 102		Cluster 4 n= 50		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p-value ***
Age (years)	20.8	2.4	21.5	3.0	21.2	2.6	21.0	2.8	0.26
BMI (kg/m^2)	22.7	3.3	23.6	3.9	23.5	3.1	23.1	2.9	0.15
Age at menarche (years)	12.7	1.4	12.2	1.4	12.3	1.5	12.3	1.3	**0.02**
Physical activity (MET/wk)	50.1	42.9	60.9	61.6	57.0	54.7	52.1	48.4	0.40
IDAS Score	33.1	8.9	38.7	9.8	37.2	8.1	46.0	10.9	**<0.001**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**p-value ***
Race : White	160	86%	59	79%	87	85%	34	68%	**0.02**
Hispanic	14	7%	5	7%	4	4%	5	10%	0.51
Education: Some/Cur. College	163	87%	61	81%	84	82%	46	92%	0.26
Currently using OC	85	45%	35	47%	41	40%	25	50%	0.67
Smoking : Ever	16	9%	13	17%	12	12%	5	10%	0.23
: Current	8	4%	4	5%	3	3%	4	8%	0.53
: Marijuana	53	28%	18	24%	35	34%	15	30%	0.51
Current use Anti-Depressants	10	5%	4	5%	3	3%	7	14%	**0.05**
Current use Multivitamins	82	44%	32	43%	38	37%	15	30%	*0.37*

* P-values calculated for continuous variables using ANOVA and for categorical variables using Chi Square. Fisher's Exact Test used due to low (<5) expected cell counts.

Table 14. Characteristics of Participants Meeting Criteria for PMS (n=80) Based on Cluster Analysis, UMASS Vitamin D Study and PMS Study (2006-2014)

		Cluster 1 n= 30		Cluster 2 n= 7		Cluster 3 n= 23		Cluster 4 n= 20		
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p-value ***
Age (years)		21.0	2.6	19.6	1.2	21.4	3.1	20.7	1.6	0.39
BMI (kg/m^2)		22.5	3.9	22.7	2.2	23.0	2.7	23.7	3.3	0.64
Age at menarche (years)		12.3	1.4	12.4	0.5	12.2	1.6	12.0	1.3	0.88
Physical activity (MET/wk)		58.9	56.4	42.1	33.8	46.9	28.6	29.3	21.6	0.10
IDAS Score		36.1	7.0	38.8	7.4	43.5	5.0	39.0	7.8	*0.07*
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**p-value ***
Race	: White	25	83%	5	71%	16	70%	13	65%	0.49
Hispanic		1	3%	0	0%	3	13%	3	15%	0.41
Education: Some/Cur. College		26	87%	7	100%	19	83%	18	90%	0.77
Currently using OC		15	50%	5	71%	12	52%	10	50%	0.81
Smoking	: Ever	10	33%	0	0%	1	4%	3	15%	**0.03**
	: Current	3	10%	1	14%	1	4%	2	10%	0.72
	: Marijuana	11	37%	2	29%	7	30%	7	35%	0.98
Current use Anti-Depressants[a]		-	-	-	-	-	-	-	-	-
Current use Multivitamins		13	43%	0	0%	9	39%	7	35%	0.18

[a] Current usage of anti-depressants is an exclusion criteria for the subset of meeting criteria for PMS.

* P-values calculated for continuous variables using ANOVA and for categorical Fisher's Exact Test used due to low (<5) expected cell counts.

Table 15. Factor Pattern Scores of All Participants (n=414) Based on Cluster Analysis Results, UMASS Vitamin D Study and PMS Study (2006-2014)

Factor Patterns	Cluster 1 n=187		Cluster 2 n=75		Cluster 3 n=102		Cluster 4 n=50		p-value*
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Emotional	-0.58	0.56	1.08	0.68	-0.26	0.81	1.07	0.89	**<0.001**
Psychological	-0.23	0.58	-0.07	0.87	-0.25	0.96	1.46	1.27	**<0.001**
Physical	-0.46	0.61	-0.55	0.63	0.90	0.91	0.71	1.11	**<0.001**
Consumption	-0.42	0.75	0.34	1.11	0.27	0.91	0.50	1.21	**<0.001**

* P-values calculated for factor patterns using ANOVA.

Table 16. Factor Pattern Scores of Participants Meeting the Criteria for PMS (n=80) Based on Cluster Analysis Results, UMASS Vitamin D Study and PMS Study (2006-2014)

Factor Patterns	Cluster 1 n=30		Cluster 2 n=7		Cluster 3 n=23		Cluster 4 n=20		p-value*
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Emotional	-0.48	0.83	0.64	0.92	0.61	0.74	-0.22	1.09	**<0.001**
Psychological	-0.41	0.69	1.59	1.17	0.52	0.75	-0.54	0.72	**<0.001**
Physical	-0.58	0.66	1.31	0.59	-0.53	0.67	1.02	0.52	**<0.001**
Consumption	-0.52	1.01	-0.33	1.34	0.50	0.62	0.32	0.85	**<0.001**

* P-values calculated for factor patterns using ANOVA.

Figure 1. Symptoms and Severity Reported by All Participants (n=414) for 26 Symptoms Ordered by 'No Symptoms', UMASS Vitamin D Study and PMS Study (2006-2014)

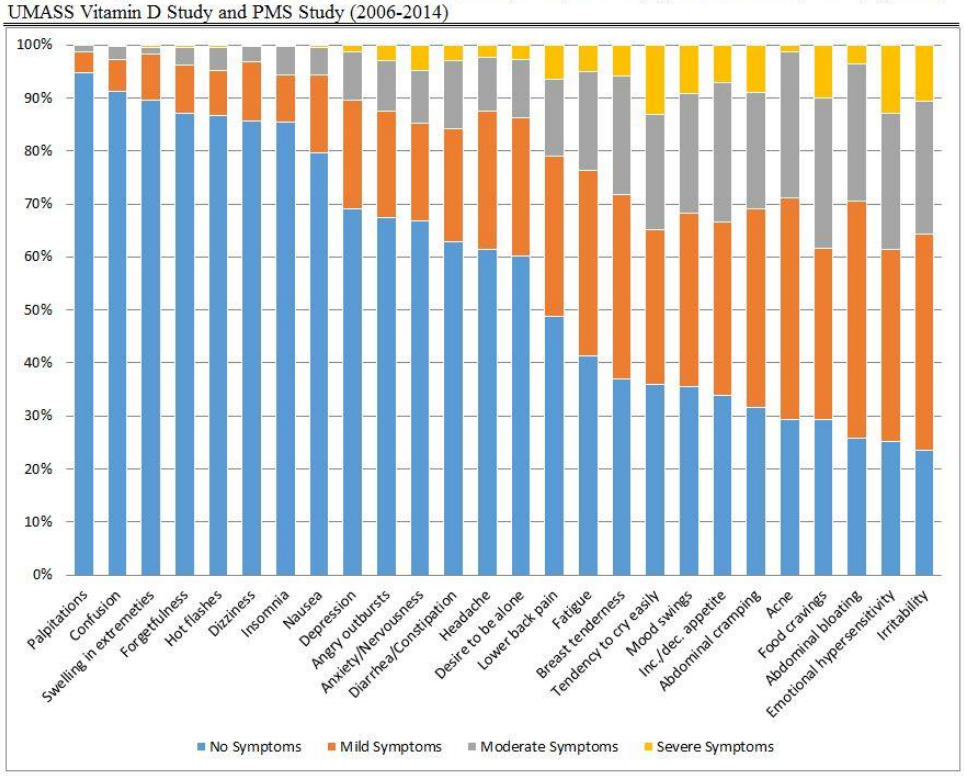


Figure 2. Symptoms and Severity Reported by Participants Meeting Criteria for PMS (n=80) for 26 Symptoms Ordered by 'No Symptoms' from All Participants, UMASS Vitamin D Study and PMS Study (2006-2014)

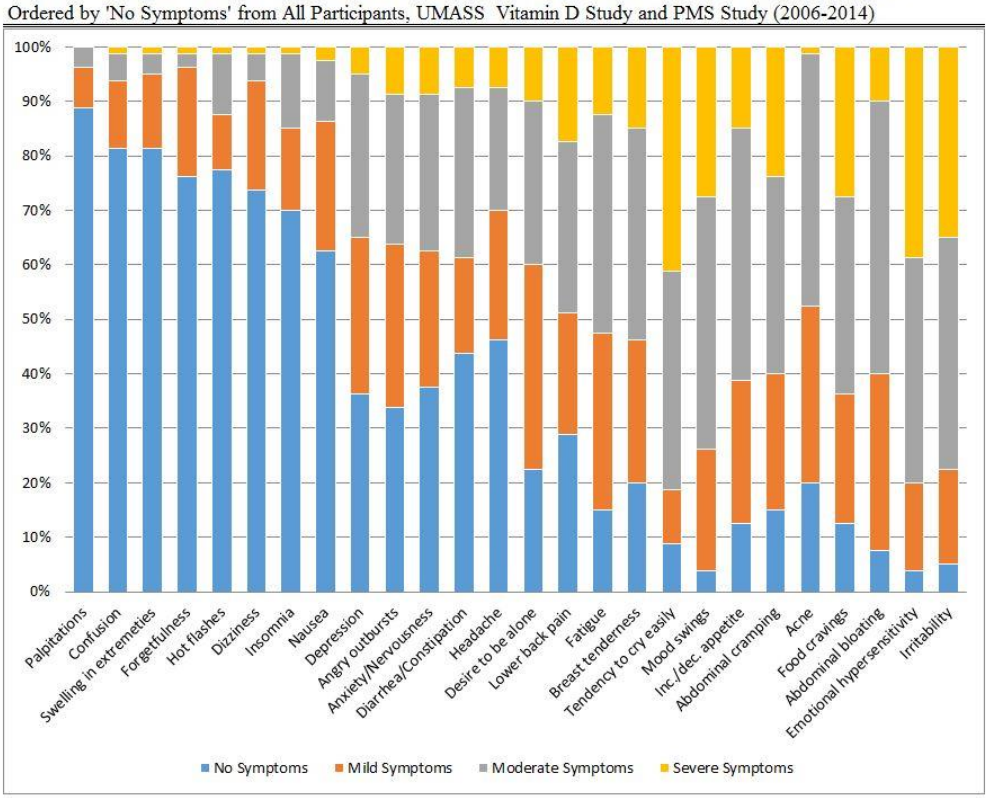


Figure 3. Parallel Analysis Scree Plot Demonstrating Simulated Eigenvalues for All Participants for 26 Symptoms, UMASS Vitamin D Study and PMS Study (2006-2014)

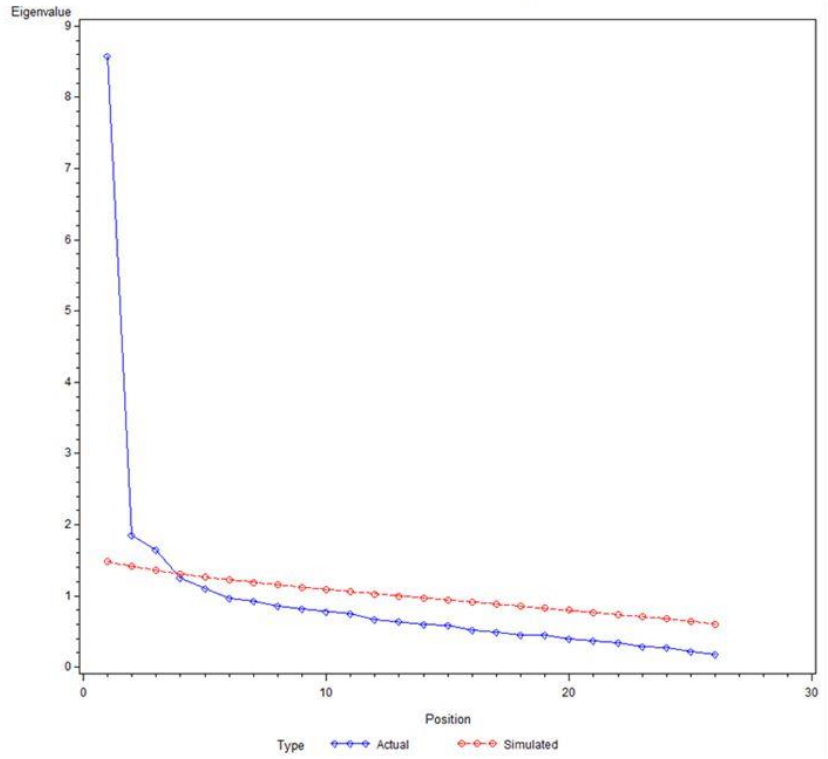


Figure 4. Parallel Analysis Scree Plot Demonstrating Simulated Eigenvalues for Participants Meeting Criteria for PMS for 26 Symptoms, UMASS Vitamin D Study and PMS Study (2006-2014)

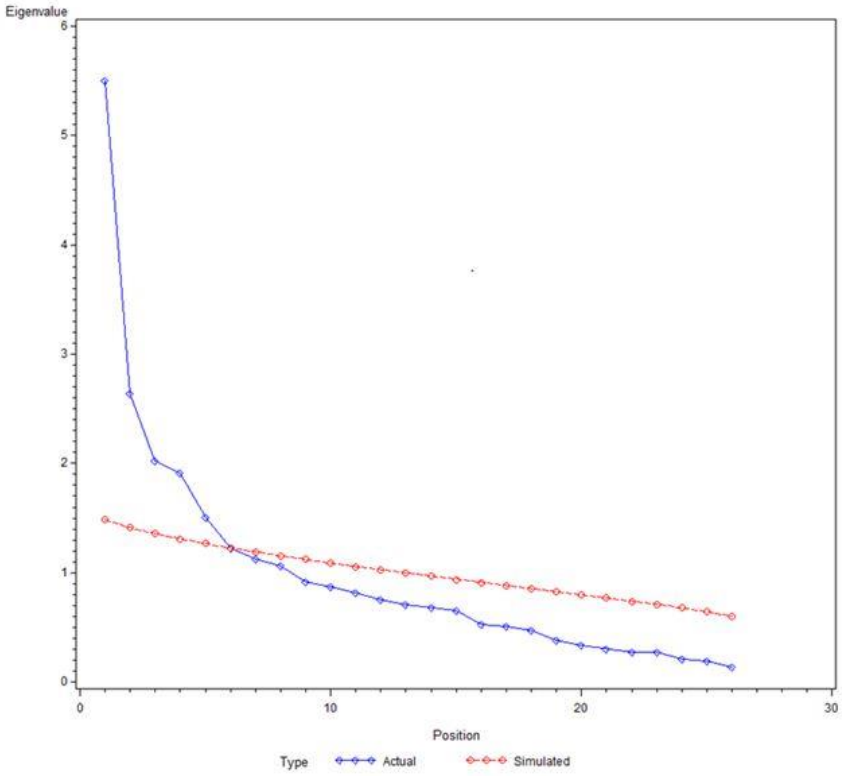


Figure 5. Cluster Analysis Results in All Participants (n=414) for 26 Symptoms, UMASS Vitamin D Study and PMS Study (2006-2014)

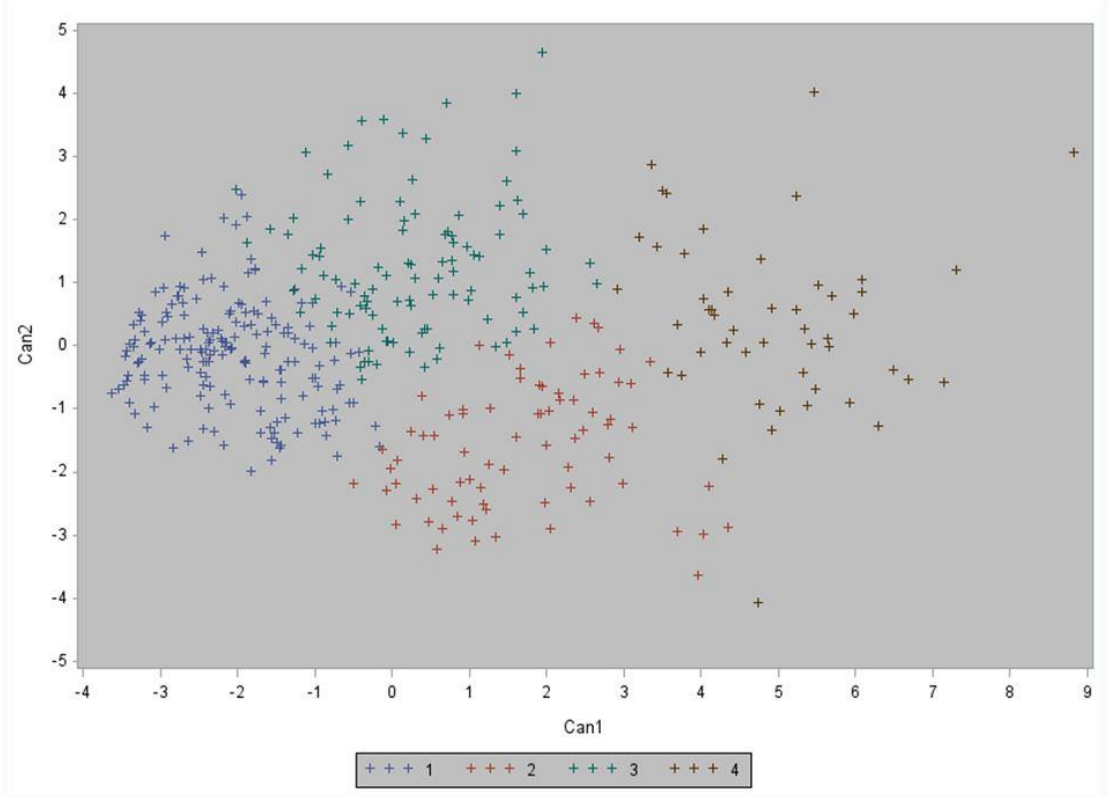


Figure 6. Cluster Analysis Results in Participants Meeting Criteria for PMS (n=80) for 26 Symptoms, UMASS Vitamin D Study and PMS Study (2006-2014)

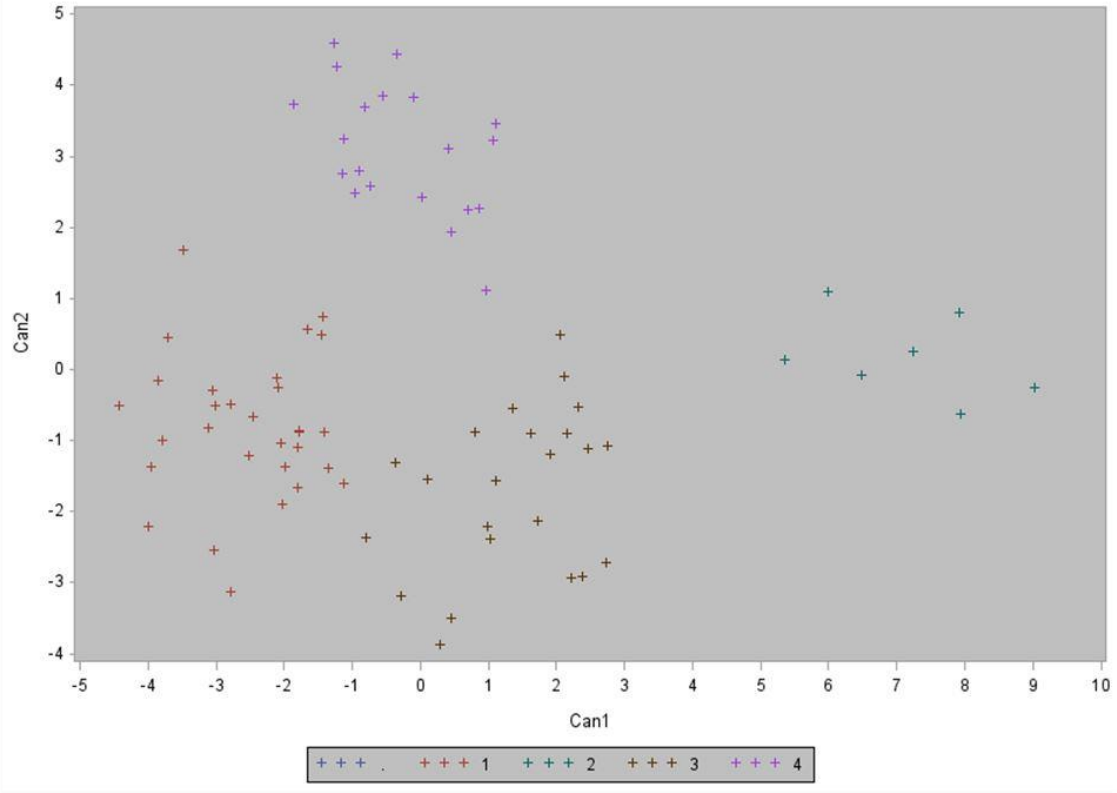


Figure 7. Cluster 1 (n=187) Symptoms and Severity Reported by All Participants, UMASS Vitamin D Study and PMS Study (2006-2014)

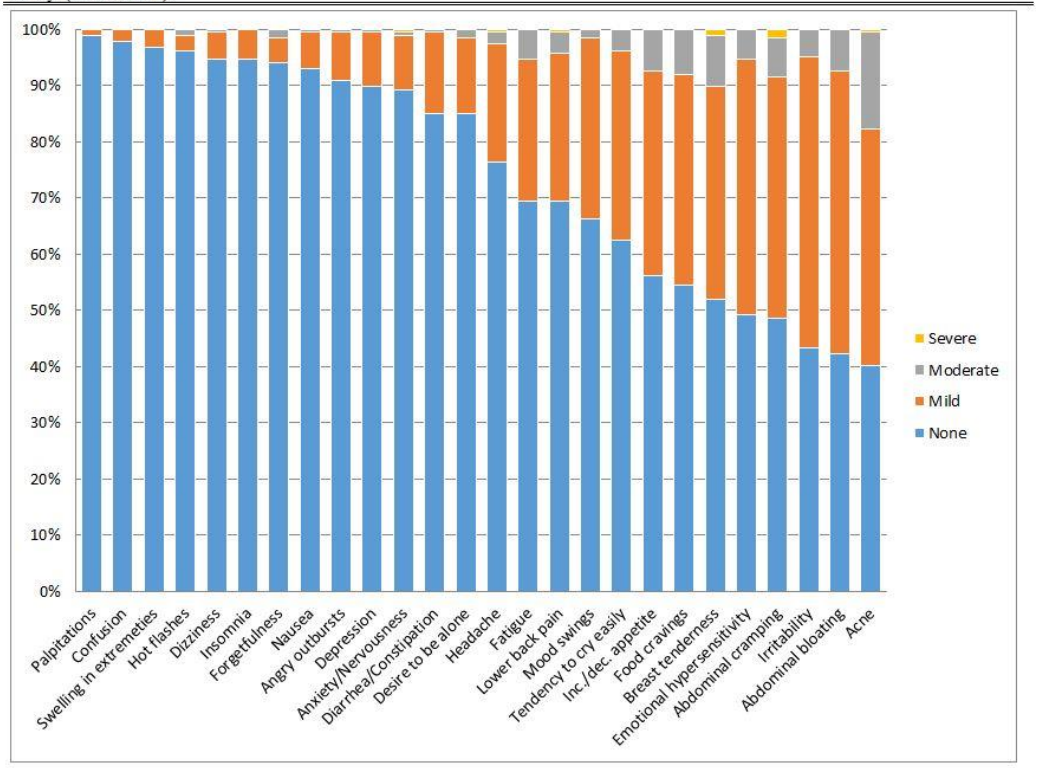


Figure 8. Cluster 2 (n=75) Symptoms and Severity Reported by All Participants, UMASS Vitamin D Study and PMS Study (2006-2014)

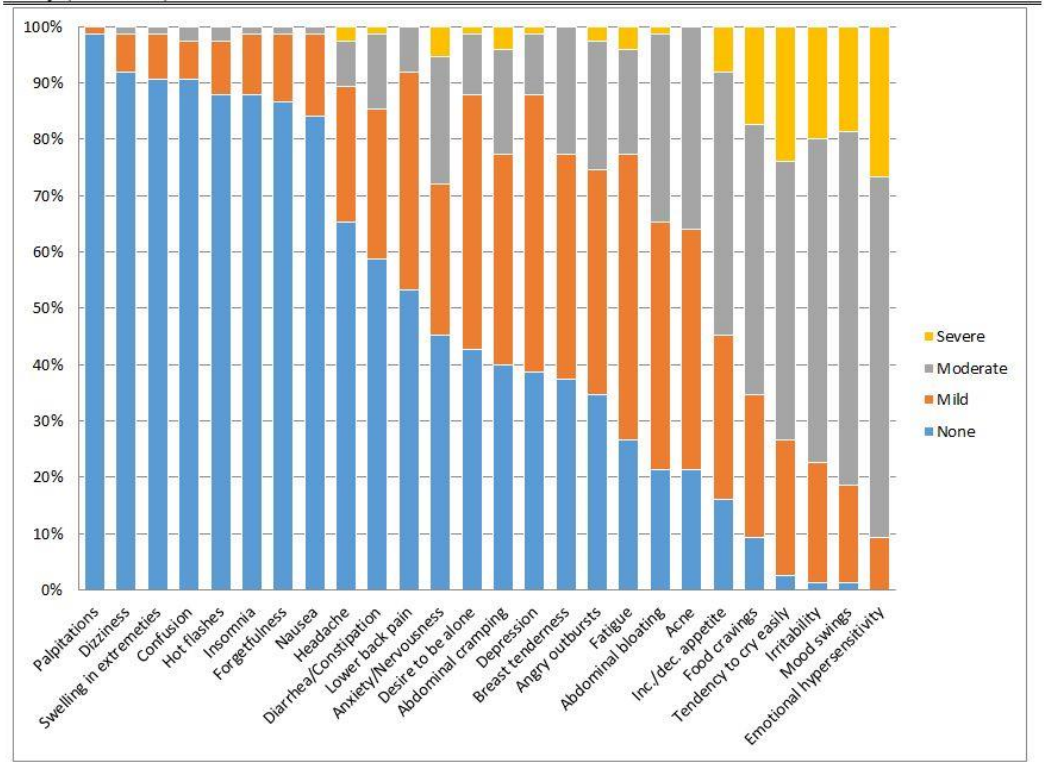


Figure 9. Cluster 3 (n=102) Symptoms and Severity Reported by All Participants, UMASS Vitamin D Study and PMS Study (2006-2014)

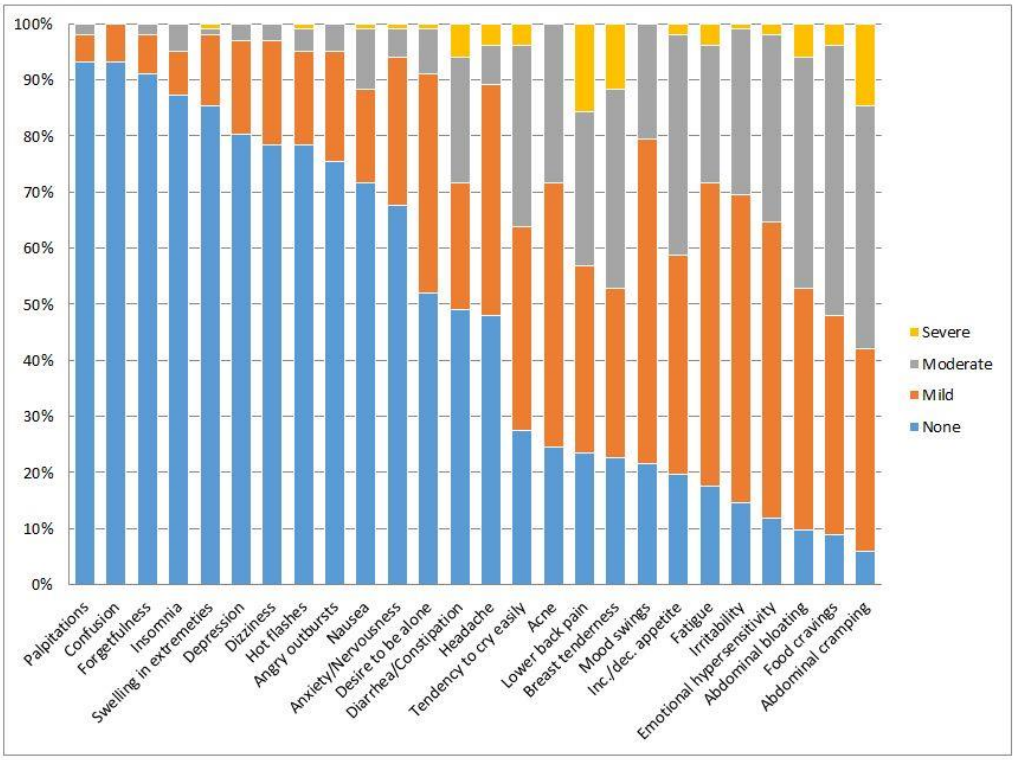


Figure 10. Cluster 4 (n=50) Symptoms and Severity Reported by All Participants, UMASS Vitamin D Study and PMS Study (2006-2014)

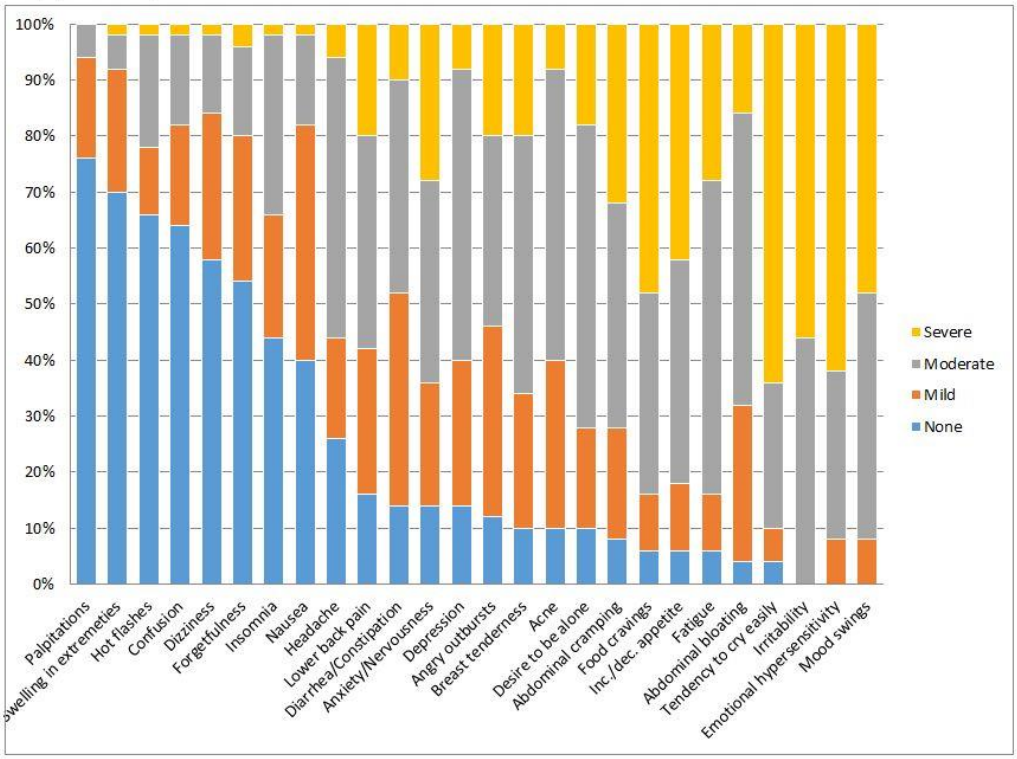


Figure 11. Cluster 1 (n=30) Symptoms and Severity Reported by Participants Meeting Criteria for PMS, UMASS Vitamin D Study and PMS Study (2006-2014)

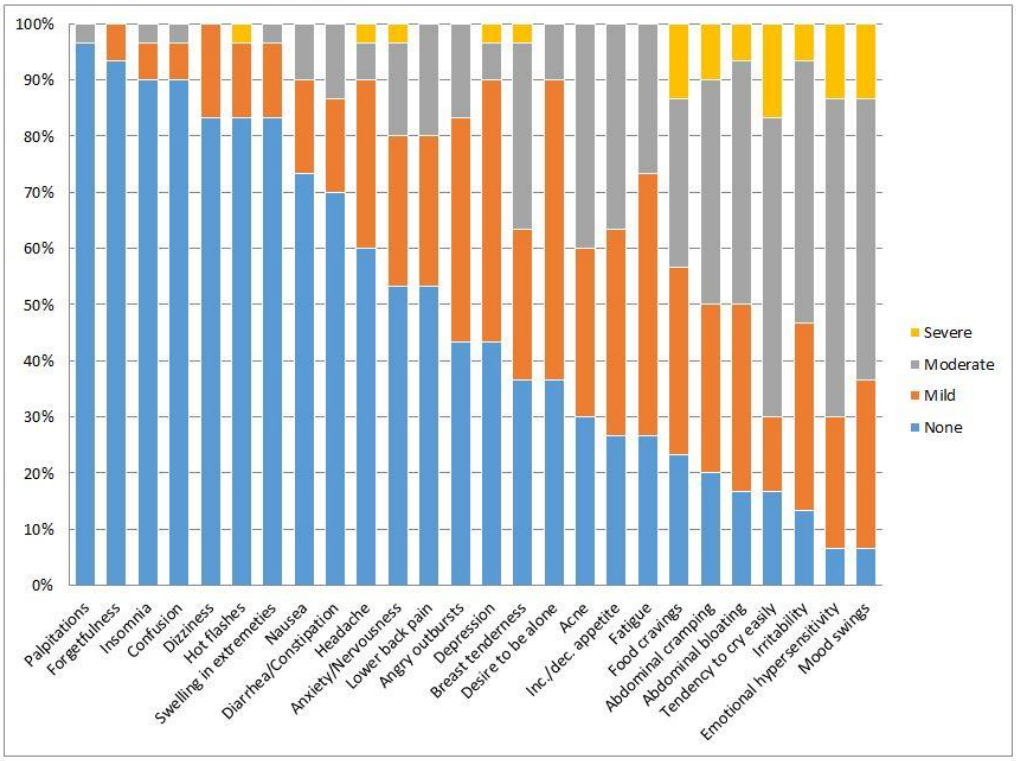


Figure 12. Cluster 2 (n=7) Symptoms and Severity Reported by Participants Meeting Criteria for PMS, UMASS Vitamin D Study and PMS Study (2006-2014)

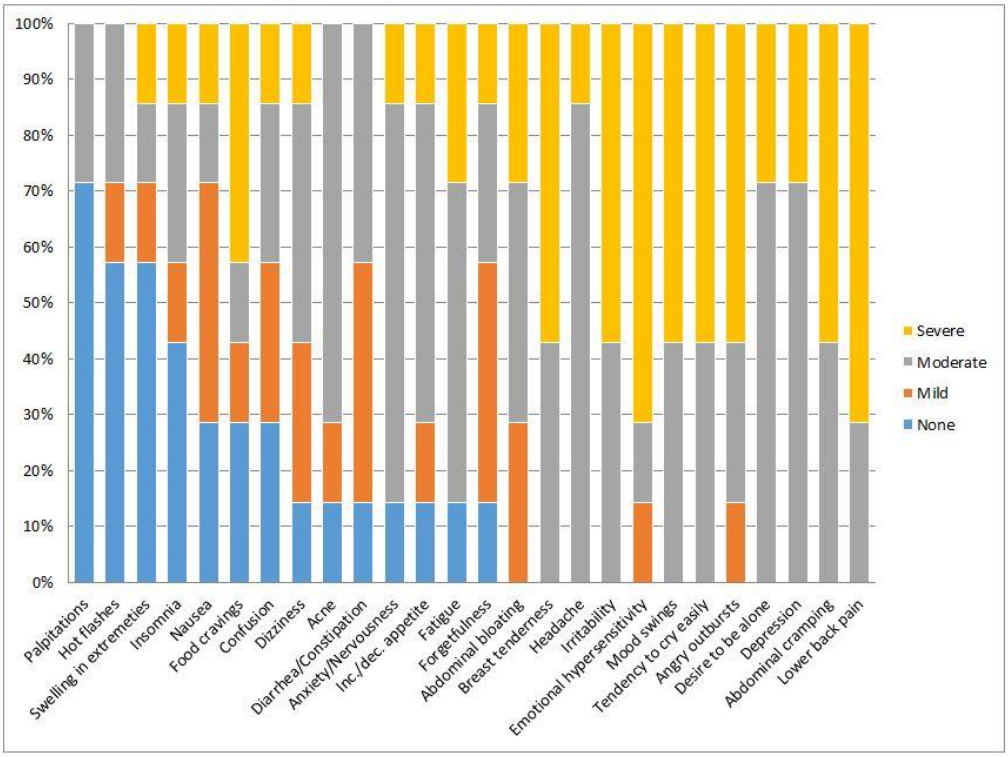


Figure 13. Cluster 3 (n=23) Symptoms and Severity Reported by Participants Meeting Criteria for PMS, UMASS Vitamin D Study and PMS Study (2006-2014)

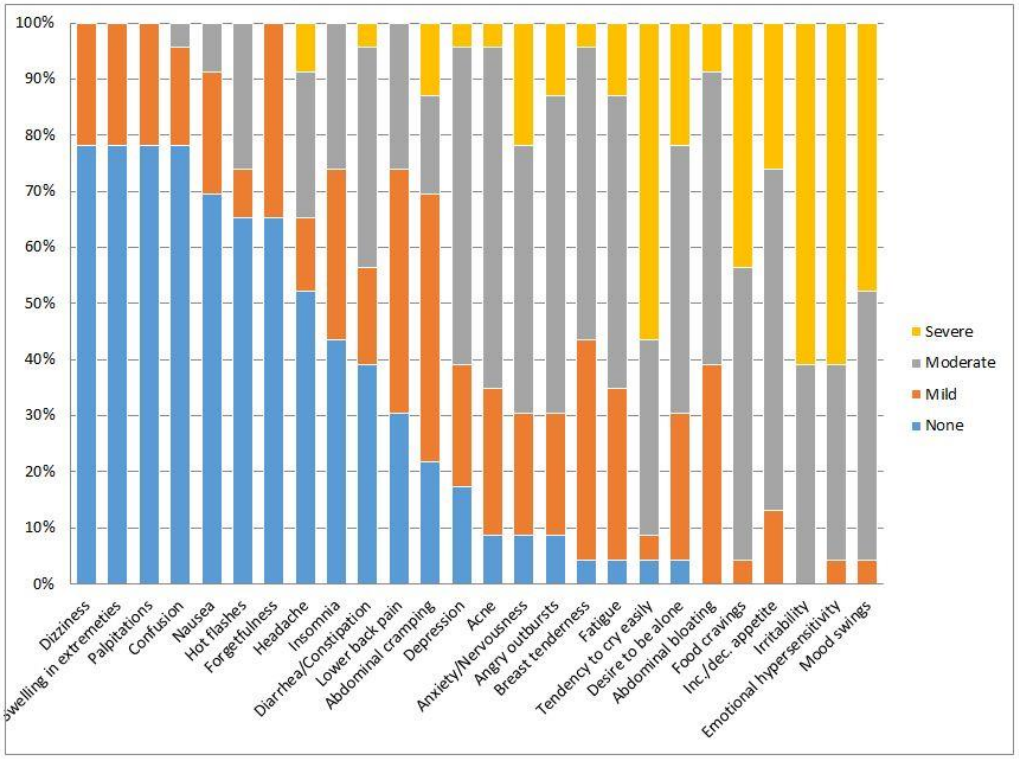


Figure 14. Cluster 4 (n=20) Symptoms and Severity Reported by Participants Meeting Criteria for PMS, UMASS Vitamin D Study and PMS Study (2006-2014)

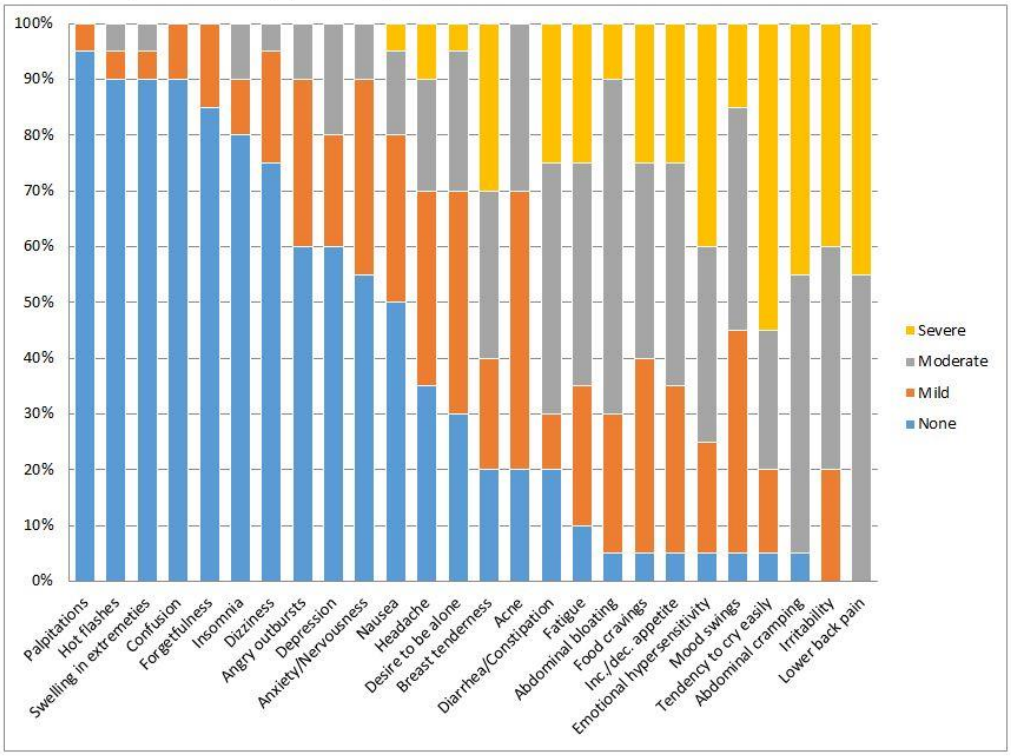


Figure 15. Distribution of Factor 1 (Emotional) Score Boxplots in All Participants (n= 414), UMASS Vitamin D Study and PMS Study (2006-2014)

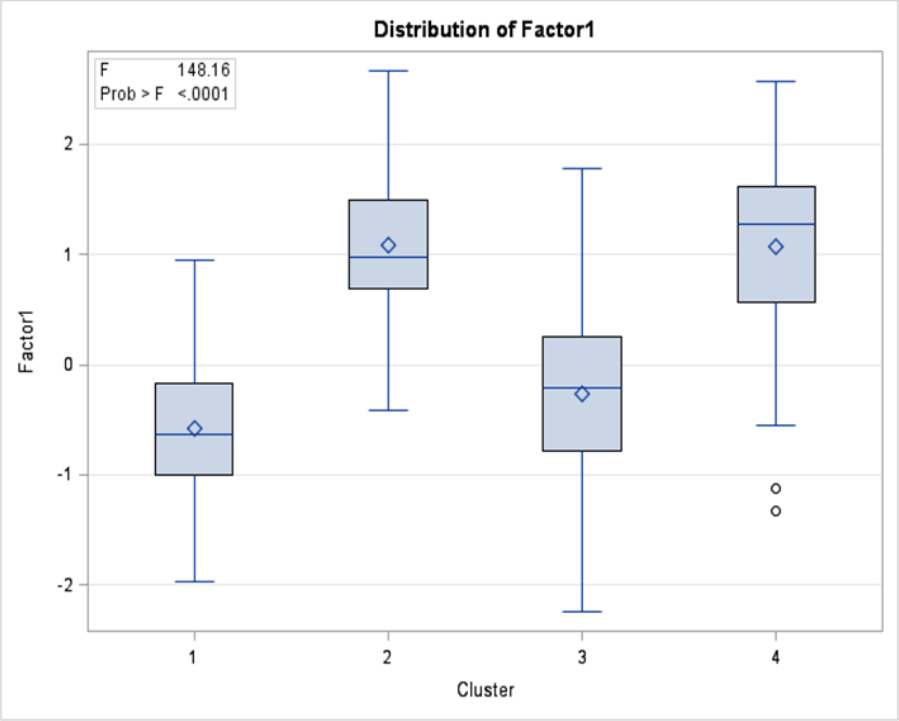


Figure 16. Distribution of Factor 2 (Psychological) Score Boxplots in All Participants (n= 414), UMASS Vitamin D Study and PMS Study (2006-2014)

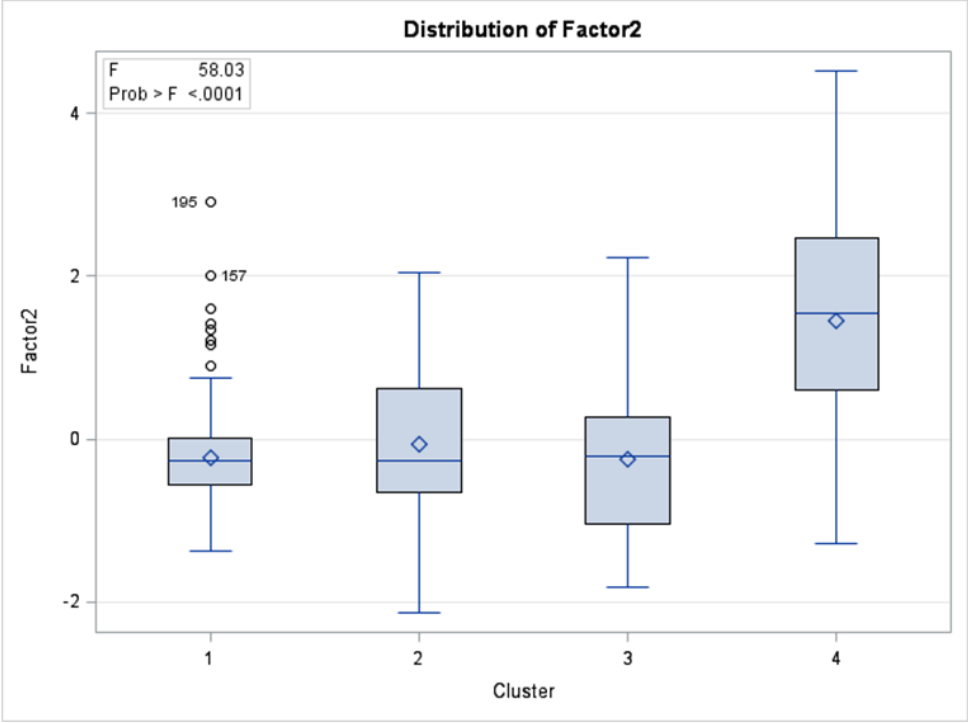


Figure 17. Distribution of Factor 3 (Physical) Score Boxplots in All Participants (n= 414), UMASS Vitamin D Study and PMS Study (2006-2014)

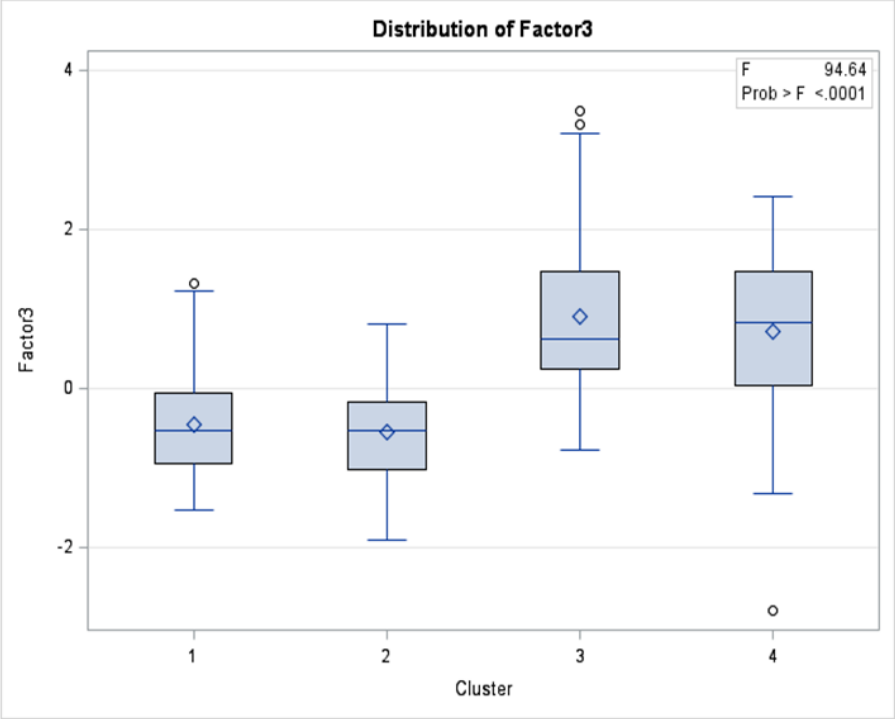


Figure 18. Distribution of Factor 4 (Consumption) Score Boxplots in All Participants (n= 414), UMASS Vitamin D Study and PMS Study (2006-2014)

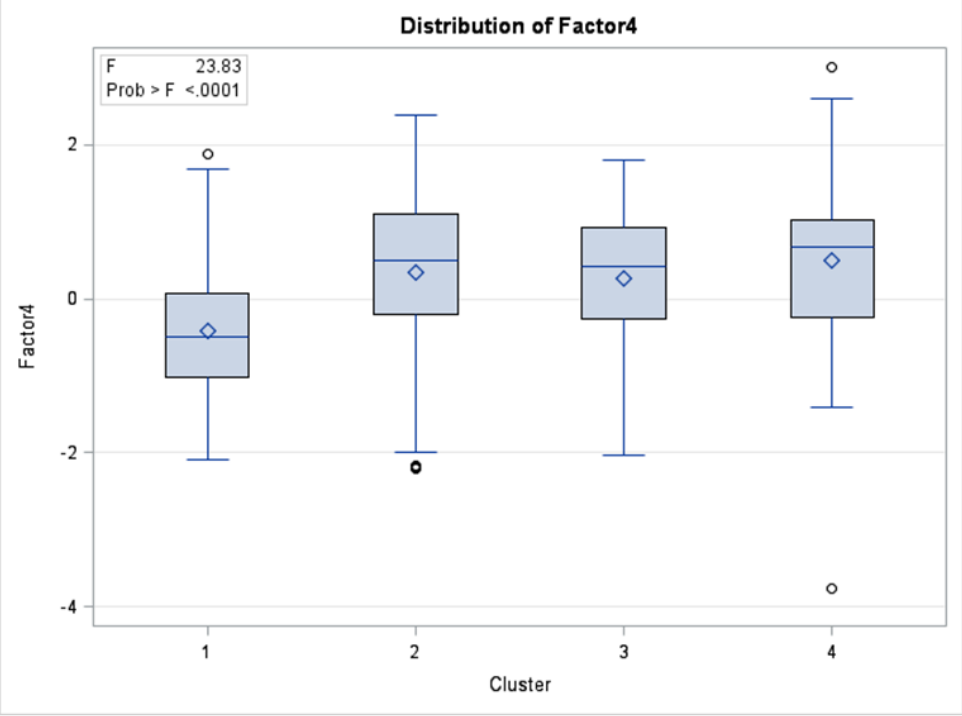


Figure 19. Distribution of Factor 1 (Psychological) Score Boxplots in Participants Meeting Criteria for PMS (n= 80), UMASS Vitamin D Study and PMS Study (2006-2014)

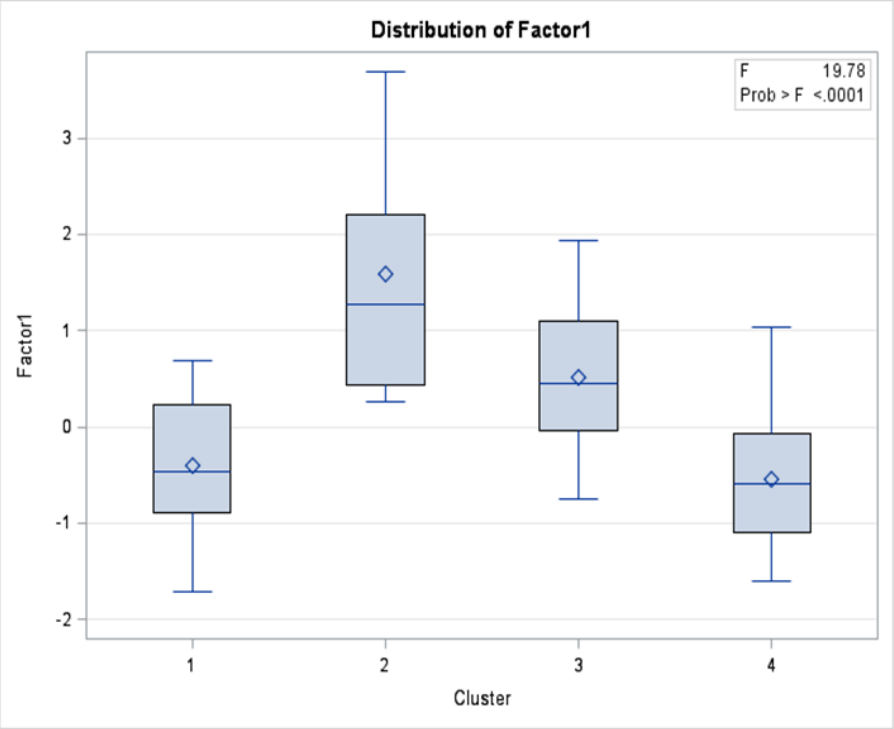


Figure 20. Distribution of Factor 2 (Emotional) Score Boxplots in Participants Meeting Criteria for PMS (n= 80), UMASS Vitamin D Study and PMS Study (2006-2014)

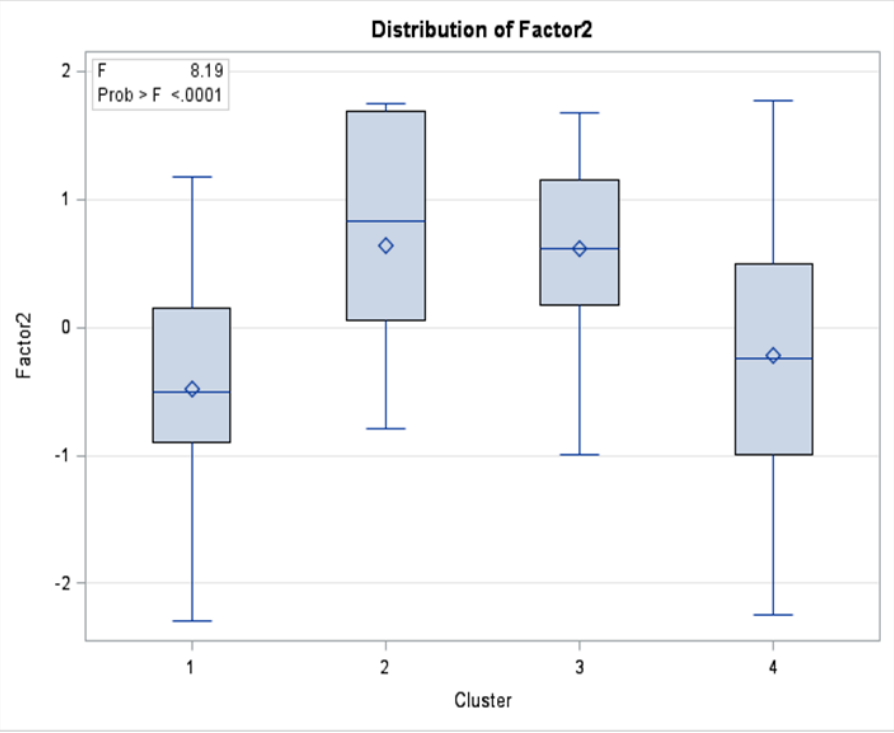


Figure 21. Distribution of Factor 3 (Physical) Score Boxplots in Participants Meeting Criteria for PMS (n= 80), UMASS Vitamin D Study and PMS Study (2006-2014)

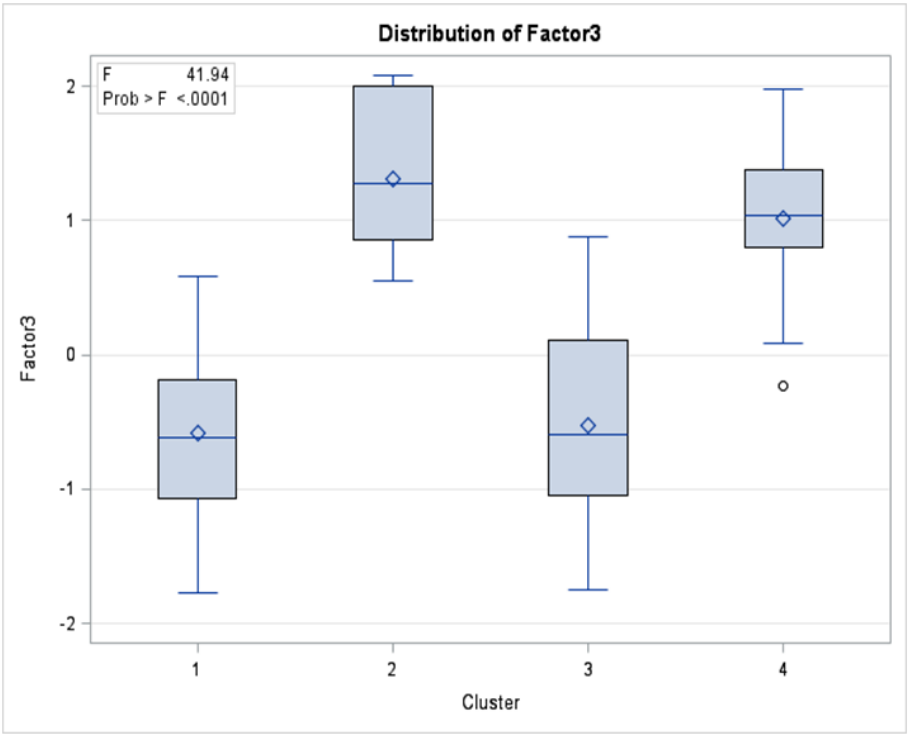
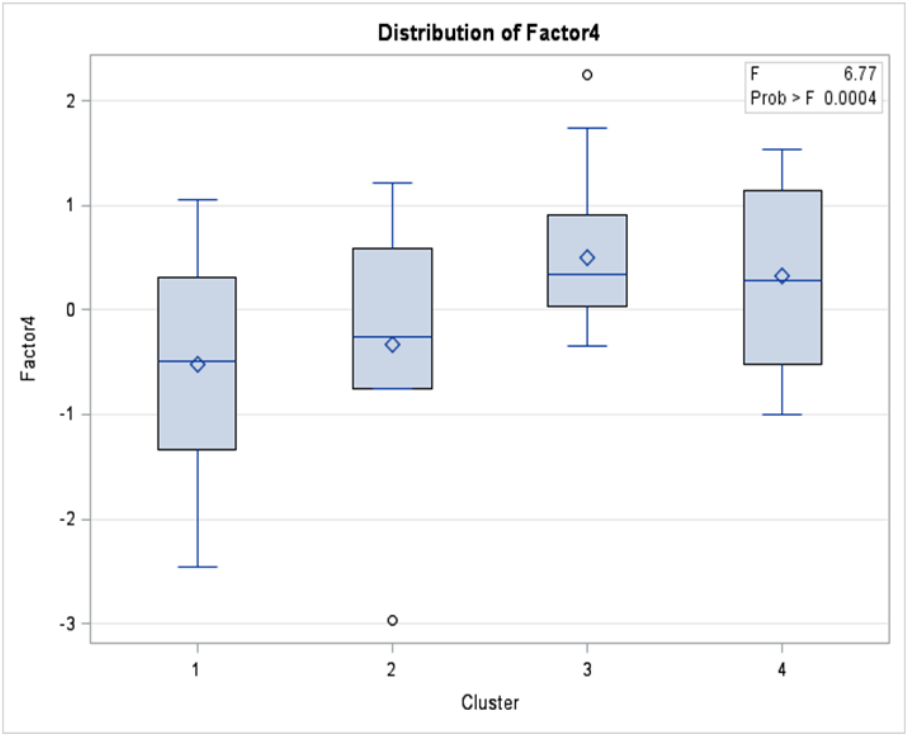


Figure 22. Distribution of Factor 4 (Consumption) Score Boxplots in Participants Meeting Criteria for PMS (n= 80), UMASS Vitamin D Study and PMS Study (2006-2014)



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